

## Original Article

# Gabapentin Pretreatment for Propofol and Rocuronium Injection Pain: A Randomized, Double-Blind, Placebo-Controlled Study

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### ABSTRACT

**Aim:** This prospectively-planned, randomized, double-blind and placebo-controlled study aims to evaluate the effect of 1200 mg gabapentin premedication on the incidence and severity of propofol and rocuronium injection pain. **Method:** One hundred patients, between 18-60 years of age and ASA I-II for elective surgery planned under general anaesthetic, were randomized and divided into two groups. Two hours before the operation, the patients were given either a placebo tablet (Group P, n = 50) or 1200 mg gabapentin tablet (Group G, n = 50). On the back of the non-dominant hand, a vein was opened using a 20 G cannula, 0.9% NaCl was begun and preoxygenation was provided. For anaesthesia induction, 1% propofol at 800 ml/hr infusion rate was administered for 20 s. Propofol injection pain was evaluated up to the 20th second and recorded using a scale between 0 and 3 developed by McCrirrick and HunteR. The remaining propofol dose (2.5 mg/kg), 5 ml saline and 0.6 mg/kg rocuronium were injected in that order over 10 seconds and rocuronium injection pain response was evaluated with a four point scale. **Results:** Pain after propofol infusion average score (degree  $\geq 1$ ) (Group G = 0.5; Group P = 1.0) and incidence (Group G = 46%; Group P = 68%); and average withdrawal movements response score linked to rocuronium injection pain ( $\geq 1$  response) (Group G = 0.3; Group P = 1.2) and incidence (Group G = 20%; Group P = 80%) were detected to be significantly lower in the gabapentin group compared to the placebo group ( $p < 0.001$ ). **Conclusion:** Premedication with 1200 mg gabapentin 2 hours before propofol and rocuronium injection reduced the incidence and severity of injection pain.

**KEYWORDS:** Gabapentin, injection pain, propofol, rocuronium

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## INTRODUCTION

Due to their rapid onset of effect and allowing rapid recovery, propofol and rocuronium are agents frequently used together in anaesthesia practice and for rapid-sequence intubation. However, both cause severe discomfort for patients due to pain in the injection arm.<sup>[1-5]</sup> During anaesthesia induction, pain, emotional stress and stimulation may cause bronchospasm, asthma and myocardial ischaemia attacks, and recoil movements linked to pain may cause injury during induction due to gastric content reflux, pulmonary aspiration and pulling the venous catheter out of place.<sup>[5,6]</sup> This may prevent the use of both agents together in clinical practice

To prevent injection pain linked to propofol, many methods and medications have been used such as using a tourniquet or adding lidocaine to propofol before applying the tourniquet, changing the pH of propofol, and administration of opioids, ondansetron, granisetron, nafamostat, magnesium sulfate, dexmedetomidine and ketamine before injection.<sup>[2-5]</sup> For prevention of rocuronium injection pain, the efficacy of many

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medications and methods have been researched, including intravenous local anaesthetics (lidocaine), opioids (fentanyl, remifentanyl), ondansetron, dexmedetomidine, magnesium sulfate, antihistamines, ketamine and dilution with 0.9% NaCl.<sup>[2-5]</sup> While the definite pathophysiological mechanism of propofol and rocuronium injection pain is not known, studies on suppressing injection pain linked to both agents by single drug premedication have shown that use of an agent with both peripheral and central antinociceptive effect has an increased chance of success.<sup>[2-5]</sup>

Gabapentin is a new-generation anti-epileptic produced to treat intractable partial convulsions which has simultaneously antinociceptive, analgesic and antihyperalgesic properties. The most widespread use of gabapentin, outside of epilepsy, is neuropathic pain. Recently, several clinical studies evaluating the potential role of gabapentin in the perioperative period for a variety of aims have been published.<sup>[7]</sup> Yoon Sun *et al.*<sup>[8]</sup> reported that premedication with gabapentin reduced the incidence and severity of recoil movements linked to rocuronium injection pain. Along with this during our literature scan, we did not find any study evaluating the effect of gabapentin premedication on propofol injection pain. The hypothesis of our study is that gabapentin premedication, with both central and peripheral antinociceptive properties, may reduce the pain of propofol injection along with rocuronium injection pain.

This prospectively-planned, randomized, double-blind and placebo-controlled study aims to evaluate the effects of 1200 mg gabapentin premedication on incidence and severity of propofol and rocuronium injection pain.

## MATERIALS AND METHODS

This study received permission from Firat University Medical Faculty Medication Research Local Ethics Committee (Prof. Dr. Mehmet Tokdemir, chairman, date 12.07.2012, decision no. 06). The study was completed through surgeries of Firat University Medical Faculty and Okmeydani Education and Research Hospital after receiving informed consent from patients between 12.11.2012 and 15.03.2013. With physical condition classified as I-II risk group according to the American Society of Anesthesiologists (ASA), 100 adult patients with elective surgical interventions planned under general anesthesia between 18-60 years of age were included in the study.

Exclusion criteria included patients; considered to have airway management difficulties; with body mass index > 25 kg/m<sup>2</sup>, cardiac disease, diabetes mellitus, impaired renal status, liver failure, COPD and asthma, hiatal hernia and symptomatic gastro-esophageal reflux,

gastrointestinal disorder affecting absorption of oral treatments, allergy to eggs and study drugs, neurological dysfunction or previous trauma history in the study hand, pregnant, breastfeeding women, drug or alcohol addiction; use of analgesic medication, aminoglycoside group antibiotics and calcium channel blockers in the previous 24 hours; history of chronic use of opioids, tricyclic antidepressants, benzodiazepine anticonvulsants, clonidine, beta blockers and systemic and/or topical steroids. No patient premedicated.

Patients were randomly divided into 2 groups with the aid of a computer (both groups n = 50). Two hours before the operation the study medications were taken by the patients with a little water, given by an anaesthetist not included in the study. Group P (placebo, n = 50) cases were given an oral placebo tablet while Group G (gabapentin, n = 50) were given an oral tablet of 1200 mg gabapentin (Neurontin® capsule 400 mg Pfizer İlaçları Ltd. Şti, Turkey). To provide a double-blind feature to the study, the study medications were prepared by a pharmacist and allocated an appropriate code number. The anaesthetist assigned to the patients, patient management and data collection was unaware of these groups. Until being taken to the operation room, nausea, vomiting, dizziness, headache, drowsiness, weakness, fatigue, nystagmus, rash, somnolence, sedation, peripheral edema, visual disturbances and any other side effects which developed in the patients were recorded.

After patients were on the operating table, preoxygenation was administered 6 l/min oxygen with a mask, a vein was opened in the back of the left hand with a 20 G cannula and 7 ml/kg 0.9% NaCl fluid infusion was begun. All fluids together with study medications administered through IV and used during surgery were brought to room temperature, and used within 30 minutes of preparation. Arterial blood pressure, heart rate (HR) and peripheral oxygen saturation (SpO<sub>2</sub>) were recorded before induction, before intubation and after the 1st, 3rd and 5th minute of intubation. After preoxygenation, for anaesthesia induction 1% propofol (Propofol 1%, Fresenius 50 ml flacon, Germany) was administered with 800 ml/hr infusion speed for 20 s. After the propofol infusion was begun until the end of the 20th second, patients were observed by an independent observer. If the patient did not complain or show any signs of pain, the patient was questioned about the same and answers were evaluated, recorded on a scale between 0-3 developed by McCrirrick and Hunter.<sup>[9]</sup> The responses were evaluated as 0 = no pain: (negative response to questioning); 1 = mild pain (pain reported in response to questioning only, no behavioural signs); 2 = moderate pain (pain reported in response to

questioning and accompanied by behavioural signs); and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).<sup>[9]</sup> After the 20th second, the remaining propofol induction dose (2.5 mg/kg), 5 ml saline and 0.6 mg/kg rocuronium (Esmeron® 50 mg.5ml-1 N.V. Organon, Oss, Holland) were injected in order over 10 seconds. After induction, the patients were manually ventilated through a mask with 100% O<sub>2</sub> so end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) was 30-35 mmHg. The movement response to rocuronium injection pain was evaluated by the same independent observer on a four point scale (FPS). The scale was 0 = no response or movement, 1 = movement of only the wrist, 2 = movement of only the arm (elbow or shoulder) and 3 = general response, movement of more than one extremity and reactions such as discomfort and pain.<sup>[8]</sup> After evaluation 1 µgr/kg fentanyl iv was administered and 2 minutes after induction, intubation was completed. Anesthesia was maintained with 2% sevoflurane and 50% NO<sub>2</sub>-O<sub>2</sub> mix. At the end of the study period, anaesthetic management was left to the anaesthesia team responsible for the operating room and aware of the medications administered.

An anesthetist blind to the medications used evaluated the injection site for any complications such as pain, swelling/puffiness or allergic reactions within 24 hours after the operation.

### POWER ANALYSIS

The major outcome of our study was determined to be the pain score after propofol. Memis *et al.*<sup>[9]</sup> in their study evaluating propofol pain determined a pain score of 1 and above in 84% of cases. Using these values to identify a 30% reduction in propofol injection pain (∅ error of 0.05 and a power of > 85%), we determined our groups should be at least 45 cases. To allow for a possibility of 10% drop-out rate the study groups comprised 50 cases.

### STATISTICS

The Statistical Package for Social Sciences (SPSS) 15.0 program was used for statistical evaluations. Frequency data such as gender, ASA distribution, cigarette and alcohol use were compared using the chi-square test. Age, body mass index, heart rate and mean arterial pressure distributions were evaluated with the Lilliefors Significance Correction and Kolmogorov Smirnov test. Age and body mass index (BMI) without normal distributions were evaluated using the Mann Whitney U test. Normally distributed data such as HR and MAP are given as mean ± standard deviation and were compared between groups using the student-t test. Repeated measurements of heart rate and mean arterial pressure were evaluated with the

Paired Sample t-test. To compare pain and movement scores between the groups, the Mann Whitney U test was used. *p* < 0.05 was accepted as significant.

### RESULTS

There was no statistically significant difference between the groups in terms of demographic data [Table 1]. There were no side effects related to gabapentin observed in any patient in Group G.

After propofol infusion, the number of patients in the gabapentin group who felt pain (degree ≥ 1) was 23 (46%) while in the placebo group, the number was 34 (68%); the incidence of pain in the gabapentin group was found to be lower, by a statistically significant degree, than in the placebo group (*p* = 0.004) [Table 2]. The average propofol pain score was significantly lower in Group G than in Group P (*p* = 0,003); identified as 0,56 ± 0,68 in Group G and 1,06 ± 0,84 in Group P.

The incidence of withdrawal movements linked to rocuronium (≥ 1 response) was significantly lower in Group G than in Group P (*p* < 0.001); observed at 20% in Group G and 80 % in Group P [Table 3]. The average

**Table 1: Demographic characteristics of patients**

Variables	Group P (n=50)	Group G (n=50)	<i>p</i>
Age (years)	30.8 ± 7.9	34.5 ± 10.7	0.056
ASA (I/II)	20/30	14/36	0.205
Body Mass Index	24.5 ± 2.4	25.9 ± 4.4	0.448
Gender (M/F)	29/21	21/29	0.110
Cigarette (user/non-user)	10/40	5/45	0.161
Alcohol (user/non-user)	3/47	8/42	0.110

Data is provided as number of patients or mean + standard deviation

**Table 2: Incidence and degree of pain on injection of propofol**

Pain score	0	1	2	3
Degree of pain	No pain	Mild	Moderate	Severe
Group G (n = 50)	27 (54%)	18 (36%)	5 (10%)	-
Group P* (n = 50)	16 (32%)	15 (30%)	19 (38%)	-

\**p* = 0.004; when compared with Group P, Chi-Square Test.

**Table 3: Incidence and degree of withdrawal movements associated with rocuronium injection**

	0	1	2	3
Group G (n = 50)	40 (80%)	5 (10%)	5 (10%)	-
Group P* (n = 50)	10 (20%)	20 (40%)	20 (40%)	-

\**p* < 0.001; when compared with Group P, Chi-Square Test.

score for rocuronium-linked withdrawal movements in Group G was  $0,30 \pm 0,65$  and in Group P was  $1,20 \pm 0,76$ ; Group G was lower by a statistically significant degree compared to Group P ( $p < 0.001$ ).

From the point of view of hemodynamic data, there was no significant difference between the groups at the measurement times. Bradycardia or hypotension was not observed in any patient. Peripheral oxygen saturation in all groups during the study period was  $\geq 97\%$ . No complications such as pain, edema, or allergic reactions were observed at the injection site within the first 24 hours after the operation.

## DISCUSSION

This study shows that administration of a single oral dose of 1200 mg gabapentin 2 hours before surgery reduced the incidence and severity of pain and withdrawal movements linked to propofol and rocuronium injection.

Propofol, which is highly oil soluble, is an irritant for the skin, mucose membranes and venous intima formed by a phenol ring added to two isopropyl groups. The onset of effect is rapid with quick recovery and few postoperative side effects, such as nausea-vomiting, headache and restlessness, which make it a nearly ideal popular intravenous anaesthetic agent for anesthesia induction and maintenance.<sup>[10]</sup> One of the most important side effects is intravenous injection pain with incidence in adults varying between 28 and 90%.<sup>[5,11]</sup> Macario *et al.*<sup>[12]</sup> study evaluating postoperative complications after routine surgical procedures reported propofol injection pain was 7th out of 33 low morbidity results.

Peripheral veins are innervated by polymodal nociceptors; this means that during administration, medications with non-physiological osmolality or pH values can directly contact the free nerve endings leading to pain.<sup>[13]</sup> Bradykinin is a powerful endogenous mediator that activates polymodal nociceptors in humans. When the medication contacts the vein endothelium the kinin cascade activation and release of endogenous algogenic mediators stimulates the chemonociceptors indirectly and causes pain.<sup>[14]</sup> The etiology of pain caused by propofol and rocuronium administration is not clear. It has been proposed that pain may be linked to chemonociceptor activation directly linked to the solution pH, osmolality and amount of free agents in the emulsion aqueous phase or indirect activation by histamine, bradykinin and other substances mediating inflammation.<sup>[1,5,14,15]</sup> Propofol injection pain may start immediately after injection or later. Delayed pain, described as coldness, numbness or serious burning pain proximal to the injection site, occurs 10-20 seconds after the injection and ceases when the injection ends.<sup>[11,15]</sup> While sudden pain is probably linked

to direct irritant effects, it is thought that pain that starts later is due to the indirect effect resulting from kinin cascade.<sup>[1,16]</sup> Despite this discomfort the incidence of venous sequelae such as phlebitis is less than 1%.<sup>[15]</sup>

There are many factors that affect the incidence and severity of pain linked to propofol injection. These include the site of the injection, the width of the cannula, the diameter of the vein, the speed of injection, concentration of propofol in the aqueous phase, the speed of fluids given, chemical structure of the injector, temperature of the propofol, effect of fluids given with propofol and buffering capacity of the blood.<sup>[16-19]</sup> On thoroughly analyzing the previous studies, our study standardized the injection site, cannula width and injection speed by using a 20 G venous catheter in the back of the left hand of all patients and using a pump to keep propofol infusion at a steady rate. To evaluate any delayed pain reaction to propofol, pain was evaluated up to the 20th second after injection. The incidence of pain linked to propofol injection in the placebo group was 68%, comparable to previous study results.<sup>[1,4]</sup> In addition, during the postoperative period when pain, erythema, or skin changes were questioned, no changes were observed in any patient.

Gabapentin is a new-generation single anti-epileptic with antinociceptive, analgesic and antihyperalgesic properties.<sup>[20]</sup> While previous studies have only shown gabapentin to have central anti-allodynic effect, it has been shown to inhibit ectopic discharge activity in injured peripheral nerves.<sup>[21,22]</sup> The anti-allodynic effects proposed for gabapentin are CNS effects (potentially at the spinal cord or brain levels) linked to increased inhibitor input (the excitators reduce input levels) in GABA-mediate pathways; antagonism of NMDA receptors and; antagonism of calcium channels and inhibition of peripheral nerves in the CNS.<sup>[23]</sup>

There are many studies in literature reporting that gabapentin is effective in control of acute and chronic postoperative pain and in reducing postoperative opioid use.<sup>[24-26]</sup> Turan *et al.*<sup>[27]</sup> reported 1200 mg oral gabapentin administration 1 hour before hand surgery under intravenous regional anesthesia reduced tourniquet pain. Yoon Sun *et al.*<sup>[8]</sup> reported that 600 mg single-dose oral gabapentin 2 hours prior to operation reduced the incidence (Group C = 55%, Group G = 28.6%) and severity (degree  $\geq 2$  movement response Group C = 47.5% and Group G = 28.5%) of movement response linked to rocuronium. Racheal *et al.*<sup>[28]</sup> in a meta-analysis evaluating the effect of gabapentin premedication on postoperative analgesia decided that 1200 mg total gabapentin premedication was more effective in reducing analgesic needs than 300 or 400 mg gabapentin. As

a result in our study, we used 1200 mg single dose gabapentin premedication, reported to provide effective results for postoperative analgesia. Similar to previous studies,<sup>[8]</sup> our premedication with gabapentin reduced the incidence (Group P = 80%, Group G = 20%) and severity (degree  $\geq 2$  motion response, Group P = 40%, Group G = 10%) of the withdrawal movements response to rocuronium. In addition, in our study the incidence of withdrawal movements to rocuronium in the control group was higher compared to Yoon Sun *et al.*'s<sup>[8]</sup> study which may be due to differences in the subject age group and number of female patients. Also, the lower withdrawal movements to rocuronium in the gabapentin group may be due to our use of a higher dose of gabapentin.

To prevent propofol injection pain, many methods and medications have been used. Among these, lidocaine holds a special place due to fewer side effects and being economical.<sup>[1,29]</sup> However while lidocaine is the most frequently used IV agent, it has a failure rate between 13 and 32%.<sup>[1]</sup> Jalota *et al.*<sup>[29]</sup> in a meta-analysis study including data from 25260 patients in 177 studies investigating the pharmacological and non-pharmacological methods to reduce propofol injection pain, reported that using the antecubital vein or using a tourniquet if a vein in the back of the hand is used, with propofol induction 30-120 seconds after lidocaine administration is the most effective method. Data from studies on suppression using single drug premedication with remifentanyl,<sup>[2]</sup> lidocaine,<sup>[2]</sup> ketamine,<sup>[3]</sup> ondansetron,<sup>[4]</sup> or dexmedetomidine<sup>[5]</sup> simultaneous to propofol and rocuronium injection pain, showed partial benefit was provided. Reddy *et al.*<sup>[4]</sup> reported ondansetron premedication was effective at reducing propofol and rocuronium injection pain; but it was not as effective as lidocaine. Ayoglu *et al.*<sup>[5]</sup> found single-dose dexmedetomidine premedication not effective in reducing propofol injection pain; but they found that the reduction in withdrawal movements linked to rocuronium was similar to that of lidocaine premedication. Yoon *et al.*<sup>[2]</sup> in a study evaluating the effect of remifentanyl premedication with tourniquet on propofol and rocuronium injection pain found remifentanyl was effective at reducing pain simultaneous to propofol and rocuronium injection and they reported that it was more effective at suppressing the withdrawal movements to rocuronium than lidocaine. In our study we found that gabapentin, with central and peripheral antinociceptive properties similar to remifentanyl and ketamine, simultaneously reduced the incidence and severity of injection pain of both propofol and rocuronium. This shows that to suppress the developing pain linked to both agents with a single drug premedication, an agent with both central and peripheral antinociceptive properties increases the chance of success.

In the period before surgery it is known that worries linked to anesthesia and surgery cause anxiety in 60-80% of patients.<sup>[30,31]</sup> Anxiety is related to lower pain thresholds, exaggerated severity of pain, more dramatic neuroendocrine response to stimulus and increased cardiovascular activity.<sup>[32-36]</sup> In addition, women in the reproductive era experience hormonal, physical and psychological changes due to the menstrual cycle. It is reported that during different periods of the menstrual cycle, patients show changes in requirements for anesthetic and postoperative analgesia.<sup>[36]</sup> Hanci *et al.*<sup>[36]</sup> in a study evaluating the effect of menstrual cycle on propofol and rocuronium injection pain reported that propofol and rocuronium injection pain was significantly lower in the follicular phase of the menstrual cycle as compared to the luteal phase. The primary limitation of our study is that the basal anxiety levels were not examined to standardize patients from a pain threshold point of view and despite the fact that half of the patients in our study were reproductive-age women, the stage of the menstrual cycle in female patients was not determined.

## CONCLUSION

This study found that 1200 mg gabapentin administered 2 hours before operation reduced the injection pain of propofol and rocuronium, commonly used for anaesthesia induction. During anaesthesia induction, it is a reality that many medications are used together. In addition, it is necessary to use accompanying medication generally to prevent or reduce injection pain in patients using propofol and/or rocuronium. To prevent pain linked to propofol and rocuronium, the clinical use of gabapentin with slow onset of effect and long effective duration may not be practical. However, the anxiolytic effect, the continuing contribution to hemodynamic stability after tracheal intubation, and better postoperative pain control, especially after painful procedures, together with the reduction in propofol and rocuronium injection pain, indicate that gabapentin premedication is worth considering.

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## Conflicts of interest

There are no conflicts of interest

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