Gabapentine 300 mg vs. 450 mg as anesthetic premedication for reactive hypertension, anxiety and analgesia

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Abstract

Objective: Observe the behavior of gabapentin to reduce reactive hypertension secondary to anxiety and pain in patients undergoing ophthalmic surgery as well as opioid consumption between groups. **Method:** Clinical randomized double blind controlled trial that analyzed 125 patients divided into three groups: Group A, gabapentin 300 mg; Group B, gabapentin 450 mg; and Group C, amaranth dragees as a control 2 h before the surgical procedure. Chi-squared test was used in sociodemographic variables and one-way ANOVA for continuous numeric variables. It was considered as significant a $p < 0.05$ for a study of two tails with a power of 80% beta. **Results:** Anxiety and analgesia intraoperative and postoperative had significant differences between groups. Lower consumption of opioid was found in the groups that used gabapentin. **Conclusions:** Gabapentin orally 300 or 450 mg h prior to surgery reduces pain, anxiety and postoperative opioid consumption in patients undergoing ophthalmic surgery.

KEY WORDS: Gabapentin. Reactive hypertension. Anxiolysis. Analgesia.

Introduction

Anxiety, pain and cardiovascular reactivity are factors that play a role in sustained hypertension. Although anxiolytics lack a significant response on chronic stress-related hypertension, they do act on reactive-origin acute hypertension because chronic anxiety disorders tend to be characterized by the prevalence of hypertension secondary to external stimuli, regardless of autonomous response¹.

Anxiety in the hospital setting is described as an unpleasant state of discomfort or emotional stress, of a secondary nature, which is generated by varying worries of the patient with regard to disease, hospitalization, anesthesia and the surgical event². The incidence of preoperative anxiety in adults ranges from 11 to 80%,

depending on whether the measurement is made by means of questionnaires or clinical parameters³.

In the surgical context, anxiety, also called perioperative anxiety, is influenced by the patient's perception about his/her general health status, uncertainty about the future, the type of surgery, the type of anesthesia to be used, postoperative discomfort, pain and even fear of death⁴, with all this depending on characteristics of the patient's personality in combination with the context of the surgical act⁵.

Patients who experience preoperative anxiety have an estimated 2.6-fold higher risk in the postoperative period⁶. In turn, a high degree of anxiety is associated with more pain, increased analgesic demand and poor satisfaction⁷.

There are different types of anxiety, but the one that is generated in the patient by the anesthetic-surgical

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act is a psychic and physical discomfort originating in the sensation of immediate danger, and is characterized by diffuse fear that can fluctuate from restlessness to panic⁸.

During the trans-anesthetic period, an anxious patient responds differently than a calm patient. Induction agent requirements tend to increase in anxious patients⁹ and there is predisposition to hemodynamic fluctuations secondary to autonomic reactions in the maintenance phase.

Izurieta and Jeffrey¹⁰ observed alterations such as pulmonary dysfunction, agitation and neurotic-type posttraumatic stress syndrome in hospitalized anxious patients.

Anxiety is a subjective and unpleasant emotional sensation, which turns its assessment into a difficult task¹¹. An objective assessment has to be made in order to be able to adequately treating it. This quantification can be carried out with scales that enable making an initial evaluation and verifying the effect of the administered treatments. For that purpose, there are different scales, such as the State-Trait Anxiety Inventory Questionnaire (STAI), the visual analogue scale for anxiety, Taylor's Inventory of Anxiety Situations and Responses or Hamilton's anxiety scales and, more recently, the Amsterdam Preoperative Anxiety and Information Scale (APAIS).

APAIS consists of a series of 6 questions with values ranging from 1 to 5 points for each answer; the highest score is 20 points. It has an informative subscale with values ranging from 1 to 5 points, where a score between 5 and 7 points indicates that patients do not require information; a score between 8 and 10 indicates that patients require more thorough information¹².

Perioperative anxiety represents a challenge for any anesthesiologist. In recent years, preoperative use of gabapentin has been proposed as a good option with few side-effects¹³.

The role of gabapentin has been studied in different situations, as postoperative analgesia, for post-surgical chronic pain prevention, attenuation of hemodynamic response to laryngoscopy and intubation, and prevention of nausea, vomiting, postoperative delirium and preoperative anxiolysis. Several studies reflect important areas of research in anesthesia and point at the important role of a single drug with multimodal effect¹⁴⁻¹⁶.

Gabapentin was introduced in 1993 as an adjuvant anticonvulsant for the treatment of refractory partial crises. Subsequently, its efficacy was demonstrated in a variety of chronic pain conditions, including postherpetic neuralgia, diabetic neuropathy, complex

regional pain syndrome, inflammatory pain, central pain, pain of malignant origin, trigeminal neuralgia, human immunodeficiency virus-related neuropathy and headache¹⁷. In 2002, gabapentin was approved by the US Food and Drug Administration for the treatment of postherpetic neuralgia. In the United Kingdom, gabapentin is fully-licensed for the treatment of all types of neuropathic pain. Its use has recently been extended to the management of more acute conditions, particularly in the perioperative period. Possible and diverse uses of gabapentin have so far been documented in more than 30 clinical trials^{18,19}.

Gabapentin is a structural analogue of the gamma-aminobutyric acid (GABA) neurotransmitter, the molecular formula of which is C₉H₁₇NO₂ and has a molecular weight of 171.24. It is a solid white crystal that at physiological pH is highly charged, freely soluble in acidic or basic media. Intestinal absorption is dose-dependent owing to a saturable mechanism in the intestine, with bioavailability inversely varying with the dose (after 300 and 600-mg doses it is 60 and 40%, respectively). It does not bind to plasma proteins and has a distribution volume of 0.6-0.8 L/kg; peak plasma concentration (2.7 mg/mL) is achieved at 2-3 hours after a 300-mg oral dose, and brain tissue concentration is 80% with regard to plasma level²⁰.

The anxiolytic effect is achieved by its binding to the $\alpha_2\text{-}\delta$ subunit protein of voltage-dependent calcium channels, acting as inhibitor of several excitatory neurotransmitters presynaptic release²¹.

A single gabapentin dose (300-1200 mg) administered within 2 hours prior to the start of a surgical event has been observed to decrease opiate consumption in the trans-anesthetic and post-anesthetic periods at a rate ranging from 20 to 62%. Given that hepatic metabolism and binding to proteins are low, no clinically relevant drug interactions are known²². In the study by Adam et al.²³, the most commonly observed adverse effects were sedation and dizziness.

Gabapentin preemptive use at 300-1200 mg doses 2 hours prior to surgery has been shown to improve postoperative analgesia and postoperative mobilization, as well as to decrease analgesic consumption in orthopedic surgery of the limbs²⁴⁻²⁶.

Studies conducted so far support gabapentin effect as anxiolytic and co-adjuvant in the management of reactive hypertension, although the most effective dose and with less adverse effects still remains to be determined.

The purpose of this study was to observe gabapentin effect to attenuate reactive hypertension secondary to anxiety and pain.

Method

Subjects were recruited in a single hospital and were invited to participate during the pre-anesthetic visit prior to the surgical event. Patients were scheduled for ophthalmologic surgery under regional anesthesia (retrobulbar block). Patients classified as ASA I, II and III according to the American Society of Anesthesiologists classification, scheduled for cataract surgery, vitrectomy of placement of valves under conscious sedation, of between 40 and 75 years of age, and who had not received anxiolytic, psychotropic or neuromodulator drugs within the 3 days prior to surgery were included. Patients with contraindications or allergy to gabapentin, patients with dementia, delirium or cognitive impairment discarded by screening and patients with KDOQI IV or V chronic kidney disease or liver failure were excluded.

A prospective, longitudinal, randomized, double-blind clinical trial was carried out. Patients were assigned to each group using a random number table. Drug distribution was carried out by an external investigator who did not participate in perioperative assessments. The population was divided in 3 groups and each patient randomly received two capsules of equal characteristics at least 2 hours prior to entering the operating room. One of the groups (group A) received a gabapentin capsule of 300 mg and a second capsule with no medication. The second group (group B) received two capsules of gabapentin of 300 and 150 mg. The third group (group C, control) received two capsules prepared with amaranth. All patients were administered regional anesthesia by means of retrobulbar block after sedation with midazolam and fentanyl. To this moment there is no standardized regimen for the practice of this sedation and, given the synergy and increased sensitivity of the central nervous system with both medications, initial sedation was carried out with midazolam (0.01 mg/kg) and fentanyl (1 µg/kg) minimal doses.

Pain and anxiety were assessed in each group by means of a numeric analogue scale and the response was subsequently broken down with Likert-type scales according to the reported intensity.

In case of inadequate anxiolysis (blood pressure figures > 20% from baseline at surgery initiation), midazolam was prepared to be administered in a dose-response fashion until blood pressure values that were optimal for the procedure were maintained.

The sample size was selected according to the study design, which corresponds to a two-sided hypothesis contrast with statistical significance at a p-value of 0.05

and β power of 0.80. A formula that compares proportions was used. Reports with a 57% increase with gabapentin were taken as the basis for anxiolysis. The resulting number per group was 40 patients, although considering 10% of attrition, it was increased to 45 patients per group.

For statistical analysis, descriptive measures such as simple frequencies and proportions were used. The chi-square test was used for sociodemographic variables and, for the number of groups, single-factor ANOVA was used as a parametric test or, otherwise, the Kruskal Wallis test if there was no normal variable distribution. A two-tailed p-value was considered to be significant, with a β power of 80%.

The study was approved by the Mexican Institute of Social Security Specialty Hospital Ethics and Research Committees, with registry number N-2014-3601-30.

Results

One-hundred and thirty-five patients were included, out of whom 7.4% (n = 10) were excluded; 3.7% (n = 5) belonged to the control group, 1.48% (n = 2) to the gabapentin 300 mg group and 2.22% (n = 3) to the gabapentin 450 mg group. In 4.44% of cases (n = 6), surgery was suspended by the treating department owing to causes that were foreign to the study, and in 2.96% of cases (n = 4), an anesthetic technique other than the proposed one was used. Final statistical analysis included 125 patients (Fig. 1).

Of the entire analyzed sample, 34.4% were females (n = 43) and 65.6% were males (n = 82). Average age was 59.71 ± 13.03 years. The description by clinical-demographic variables is detailed in table 1.

For the purposes of this study, reactive hypertension was defined as those sudden blood pressure increases higher than 20% from baseline (according to nursing records), with a decrease thereof after anxiolytic drugs administration. Of the entire sample, 57.6% of patients (n = 72) met the study operational definition. The percentage distribution of patients who experienced reactive hypertension by groups was the following: group A, 20% (n = 25); group B, 20.8% (n = 26); and group C, 16.8% (n = 21) ($\chi^2 = 0.657$; gl = 2; p = 0.72).

The Kolmogórov-Smirnov test showed normal distribution for hemodynamic and respiratory variables, with p-values > 0.05. Their behavior is detailed in table 2.

Anxiety

The degree of anxiety was analyzed in our study using Likert-type scales where 0 = none, 1-3 = low,

Figure 1. CONSORT flow diagram.

Table 1. Clinical-demographic variables of the study population

	Group A, gabapentin 300 mg (n = 41)	Group B, gabapentin 450 mg (n = 44)	Group C, control (n = 40)	Statistics
Gender, n (%)				
Female	18 (14.4)	43 (34.4)	13 (10.4)	$\chi^2 = 2.64$; gl = 2; p = 0.26
Male	23 (18.4)	82 (65.6)	27 (21.6)	
Age, years (X $\pm$ SD)	59.9 (13.9)	60.27 (13.6)	58.9 (11.6)	t = 0.12; gl = 2; p = 0.886
BMI (X $\pm$ SD)	27.4 (4.7)	27.2 (4.7)	27.3 (4.4)	t = 6.90; gl = 8; p = 0.547
Endocrinopathies (%)				
Diabetes mellitus				$\chi^2 = 0.91$; gl = 2; p = 0.634
Hypothyroidism	21 (16.8)	27 (21.6)	22 (17.6)	
Cardiopulmonary (n, %)	2 (1.6)	1 (0.8)	0 (0)	$\chi^2 = 3.95$; gl = 4; p = 0.418
COPD, OSAS	1 (0.8)	2 (1.6)	1 (0.8)	
ACIS	2 (1.6)	0 (0)	0 (0)	$\chi^2 = 9.38$; gl = 8; p = 0.317
Arrhythmias	1 (0.8)	1 (0.8)	0 (0)	
Dyslipidemia	2 (1.6)	7 (5.6)	4 (3.2)	
Other, n (%)				
CKD	2 (1.6)	7 (5.6)	4 (3.2)	$\chi^2 = 2.78$; gl = 2; p = 0.249
Smoking	9 (7.2)	12 (9.6)	18 (14.4)	
Drug addictions	1 (0.8)	1 (0.8)	2 (1.6)	$\chi^2 = 5.49$; gl = 2; p = 0.064
				$\chi^2 = 0.71$; gl = 2; p = 0.734

ACIS: acute coronary ischemic syndrome; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; SD: standard deviation.

Table 2. Analyzed groups hemodynamic and respiratory behavior

	Group A, gabapentin 300 mg (n = 41) Mean (SD)	Group B, gabapentin 450 mg (n = 44) Mean (SD)	Group C, control (n = 40) Mean (SD)	Statistics
Heart rate (bpm)				
Baseline	70.0 (10.6)	71.5 (11.3)	72.9 (13.4)	F = 0.62; gl = 2; <i>p</i> = 0.536
Trans-operative	69.1 (10.7)	69.3 (11.9)	71.2 (11.9)	F = 0.40; gl = 2; <i>p</i> = 0.666
Postoperative	65.9 (9.3)	67.1 (11.2)	69.5 (11.7)	F = 1.18; gl = 2; <i>p</i> = 0.309
Systolic blood pressure (mmHg)				
Baseline	152.9 (23.6)	152.9 (23.6)	149.1 (31.2)	F = 0.29; gl = 2; <i>p</i> = 0.749
Trans-operative	146.7 (19.9)	139.8 (15.7)	141.5 (19.8)	F = 1.59; gl = 2; <i>p</i> = 0.734
Postoperative	140.9 (19.9)	138.1 (18.3)	132.1 (27.5)	F = 1.66; gl = 2; <i>p</i> = 0.193
Diastolic blood pressure (mmHg)				
Baseline	84.4 (10.5)	85.9 (10.8)	86.9 (9.9)	F = 0.56; gl = 2; <i>p</i> = 0.567
Trans-operative	80.1 (9.1)	78.3 (9.1)	80.2 (9.5)	F = 0.56; gl = 2; <i>p</i> = 0.571
Postoperative	77.4 (9.3)	75.5 (9.0)	77.9 (9.2)	F = 0.75; gl = 2; <i>p</i> = 0.471
Mean blood pressure (mmHg)				
Baseline	87.01 (21.2)	86.78 (24.7)	85.44 (28.6)	F = 0.47; gl = 2; <i>p</i> = 0.954
Trans-operative	79.05 (17.3)	73.31 (13.5)	76.4 (17.7)	F = 1.32; gl = 2; <i>p</i> = 0.270
Postoperative	73.39 (17.0)	69.65 (12.25)	69.34 (19.23)	F = 0.78; gl = 2; <i>p</i> = 0.459
Oxygen saturation (%)				
Baseline	92.6 (3.6)	94 (3.2)	94.0 (3.4)	F = 2.18; gl = 2; <i>p</i> = 0.117
Trans-operative	97.2 (1.7)	97.5 (1.7)	96.5 (2.7)	F = 2.62; gl = 2; <i>p</i> = 0.076
Postoperative	95.9 (12.9)	97.5 (1.8)	97.9 (1.5)	F = 0.81; gl = 2; <i>p</i> = 0.446
Respiratory rate (bpm)				
Baseline	16.4 (1.2)	16.5 (1.0)	16.4 (0.9)	F = 0.076; gl = 2; <i>p</i> = 0.927
Trans-operative	16.6 (1.3)	15.9 (1.7)	16.2 (1.0)	F = 2.30; gl = 2; <i>p</i> = 0.104
Postoperative	16.1 (1.5)	16.2 (1.1)	16.1 (0.8)	F = 0.072; gl = 2; <i>p</i> = 0.930

4-6 = moderate and 7-10 = severe. Assessments were carried out at the following moments: baseline measurement just before the first dosing of the study medication, the second during operating room initial monitoring and finally at immediate postoperative period. This variable was analyzed using Kruskal-Wallis test, which yielded a *p*-value = 0.310 for preoperative anxiety, *p* = 0.01 for trans-operative anxiety and *p* = 0.002 for postoperative anxiety. Subsequently, an analysis was carried out with the chi-square test in order to see the percentage distribution by groups in detail (Table 3).

Conversely, no significant differences were found in total midazolam consumption during the surgical procedure, with means reported at 0.63 ± 0.55 mg (group A), 0.56 ± 0.63 mg (group B) and 0.74 ± 0.55 mg (group C) (*F* = 0.942; *gl* = 3; *p* = 0.393).

Pain

Pain was measured by means of a clinimetric technique using the numeric analogue scale. Similarly, the patient sample was divided into those without pain (0 points), with pain of mild-moderate intensity (1-4

points) and with intense pain (> 5 points). Assessments were carried out at two moments: immediately after retrobulbar block and after admission to the post-anesthetic care unit. Analysis with the Kruskal-Wallis test reported statistically significant differences between groups at both measuring moments, with *p* = 0.003 and *p* = 0.000, respectively. Similarly, details in pain reports using Likert-type scales for statistical analysis with the chi-square test are shown in table 4.

Fentanyl total consumption during the surgical procedure was 98.17 ± 30.8 µg (group A), 107.05 ± 26.8 µg (group B) and 119.32 ± 35.70 µg (group C), with statistically significant differences (*F* = 3.80; *gl* = 2; *p* = 0.025).

Discussion

The use of gabapentin in our study to reduce the presence of reactive hypertension failed to demonstrate clinically or statistically significant differences in patients undergoing ophthalmic surgery. In addition, with the administered doses, important modifications in hemodynamic and respiratory behavior appear not to occur behavior before and after surgery, which is

Table 3. Likert anxiety degree in the groups

	Group A, gabapentin 300 mg n (%)	Group B, gabapentin 450 mg n (%)	Group C, control n (%)	Statistics
Preoperative				
None	3 (2.4)	4 (3.2)	1 (0.8)	$\chi^2 = 6.92$; gl = 6; $p = 0.328$
Low	21 (16.8)	14 (11.2)	15 (12.8)	
Moderate	12 (9.6)	22 (17.6)	16 (12.8)	
Severe	5 (4.0)	4 (3.2)	7 (5.6)	
Trans-operative				
None	23 (18.4)	12 (9.6)	9 (7.2)	$\chi^2 = 17.25$; gl = 6; $p = 0.008$
Low	16 (12.8)	22 (17.5)	19 (15.2)	
Moderate	2 (1.6)	9 (7.2)	12 (9.6)	
Severe	0 (0)	1 (0.8)	0 (0)	
Postoperative				
None	32 (25.6)	23 (18.4)	16 (12.8)	$\chi^2 = 15.66$; gl = 6; $p = 0.016$
Low	8 (6.4)	21 (16.8)	22 (17.6)	
Moderate	1 (0.8)	0 (0)	1 (0.8)	
Severe	0 (0)	0 (0)	1 (0.8)	

Table 4. Analyzed groups pain report

	Group A, gabapentin 300 mg	Group B, gabapentin 450 mg	Group C, control	Statistics
Retrobulbar block, n (%)				
Absent	34 (27.2)	28 (22.4)	16 (12.8)	$\chi^2 = 19.62$; gl = 4; $p = 0.001$
Mild-moderate	7 (5.6)	14 (11.2)	17 (13.6)	
Severe	0 (0)	2 (1.6)	7 (5.6)	
PACU, n (%)				
Absent	40 (32)	37 (29.6)	23 (18.4)	$\chi^2 = 24.06$; gl = 4; $p = 0.000$
Mild-moderate	1 (0.8)	6 (4.8)	17 (13.6)	
Severe	0 (0)	1 (0.8)	0 (0)	

PACU: post-anesthetic care unit.

consistent with previous publications where gabapentin has been used as premedication in cataract surgeries at much higher doses (1200 mg), although in the study by Azeem and Marey²⁷, even when there was a trend towards lower blood pressure values in the gabapentin group, no statistically significant differences were found. Similarly, in a controlled clinical trial where gabapentin (900 mg) was used as premedication for nose and larynx surgery, no significant modifications were observed in hemodynamic and respiratory behaviors, a similar situation to that observed in our study²⁸. We also failed to find any reason for a trend towards higher blood pressure values to exist in the groups that used gabapentin. Given the above, it is possible that the employed doses were insufficient to reduce the sympathetic response that is reflected on a transient increase in blood pressure as a consequence of the anxiety that occurs during the preoperative period.

Reactive hypertension is a response that is secondary to anxiety episodes²⁹, which is why preoperative anxiety assessment was another variable that was essential to be measured. For the measurement of the

degree of anxiety, we proposed using the standardized questionnaire of the APAIS scale, a scale that is often used in perioperative anxiety studies; however, it has not been validated in Spanish³⁰ and for this reason we used Likert-type scales. On the other hand, Ménigaux et al.³¹ demonstrated in a controlled clinical trial that the use of gabapentin in the preoperative period produces a statistically significant anxiety decrease. Anxiolysis benefits have also been reported in psychiatric disorders such as panic attacks²⁷. However, the exact mechanisms by means of which gabapentin exerts its anxiolytic effect have so far not been described; a possible route is an increase in the GABA neurotransmitter synthesis by regulating enzymes³². In this study, a greater anxiolytic effect appears not to occur at higher gabapentin doses when 300 and 450 mg are compared, but it does with regard to the control group, and the search can therefore be started for more optimal dosages for premedication in the management of perioperative anxiolysis, especially in our population, given that it has not been explored in our country, and furthermore due to the multiple adverse effects

that often occur as a consequence of the medication the larger the employed dose is.

In another context, there has been much questioning about gabapentin analgesic mechanism, and it has been concluded that it inhibits neural transmission via voltage-dependent calcium channels, by inhibiting excitatory neurotransmitters release^{33,34}.

The use of 1.2 g of gabapentin one hour prior to surgery decreases reported postoperative pain figures, as well as opiate consumption during surgery³³. Peng et al.³⁵ concluded in a meta-analysis that gabapentin perioperative use reduces opiate total use and potentiates their analgesic effects, which translates into an important decrease of postoperative acute pain. In our study, premedication with gabapentin was shown to be useful in trans-anesthetic and post-anesthetic pain control, with lower pain perception figures being reported by the groups where gabapentin was administered in comparison with the control group, with higher opiate consumption in the latter and statistically significant differences. The authors consider that an important contribution of the study is reporting that 300-mg doses are sufficient to decrease opiate total requirements and perioperative anxiety reports, in addition that these responses are similar to those obtained when 450 mg doses are used.

Although a direct effect of gabapentin on reactive hypertension could not be demonstrated, its effects on anxiety state and analgesia were observed without important side effects being reported, except for mild somnolence.

Conclusions

The 300 or 450 mg gabapentin oral administration regimen 2 hours prior to surgery reduces pain and anxiety during immediate postoperative period, as well as opiate consumption, although it doesn't decrease reactive hypertension associated with these factors in patients undergoing ophthalmologic surgery.

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