

Pregabalin as a premedication for anxiety in patients undergoing plastic surgery: A randomized double-blind and placebo-controlled study

Pregabalina como premedicación para ansiólisis en pacientes sometidos a cirugía plástica: estudio controlado aleatorizado doble ciego con placebo

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Abstract

Objective: The objective of this study was to evaluate the usefulness of premedication with 75 mg pregabalin orally to reduce the degree of pre-operative anxiety in patients scheduled for plastic surgery procedures. **Method:** A controlled randomized double-blind clinical trial that analyzed two groups of patients: 75 mg pregabalin tablet (Pg) against placebo tablet (Pl). Efficacy was assessed using the visual anxiety scale (VAS) with two measurements, the first without medication and the second 70 min after the drug was taken. **Results:** One hundred patients were evaluated, 50 received pregabalin and 50 placebo, baseline VAS score showed an general average of 4.6 ± 1.9 points, significantly higher in the Pg group (5.2 ± 2.1 points vs. 4.1 ± 1.6 points Pl; $p = 0.0035$). The VAS score after premedication was 3.9 ± 2.1 points, significantly lower in the Pg group (3.2 ± 1.6 points vs 4.6 ± 2.3 Pl points, $p = 0.0006$). **Conclusion:** Premedication 75 mg pregabalin orally decreases the degree of pre-operative anxiety in adult patients scheduled for plastic surgery procedures.

Keywords: Anesthesiology. Anxiety. Plastic surgery. Pregabalin. Premedication.

Resumen

Objetivo: Evaluar la utilidad de la premedicación con 75 mg de pregabalina por vía oral como dosis única para disminuir el grado de ansiedad preoperatoria en pacientes sometidos a cirugía plástica. **Método:** Ensayo clínico controlado, prospectivo, aleatorizado, doble ciego, que analizó dos grupos de pacientes: pregabalina tableta de 75 mg (grupo Pg) contra tableta placebo (grupo Pl). La eficacia se evaluó utilizando la escala visual de ansiedad (Eva) con dos mediciones, la primera sin medicación y la segunda 70 min después de tomar la cápsula. **Resultados:** Se evaluaron 100 pacientes: 50 que recibieron pregabalina y 50 placebo. La puntuación basal de la Eva mostró un promedio general de 4.6 ± 1.9 puntos, significativamente mayor en el grupo Pg (5.2 ± 2.1 puntos en Pg vs. 4.1 ± 1.6 puntos en Pl; $p = 0.0035$). El puntaje en la Eva posterior a la premedicación fue de 3.9 ± 2.1 puntos, significativamente menor en el grupo Pg (3.2 ± 1.6 puntos en Pg vs. 4.6 ± 2.3 puntos en Pl; $p = 0.0006$). **Conclusión:** La premedicación con 75 mg de pregabalina disminuye el grado de ansiedad preoperatoria en pacientes que serán intervenidos de cirugía plástica.

Palabras clave: Anestesiología. Ansiedad. Cirugía plástica. Pregabalina. Premedición.

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Introduction

Pre-operative anxiety is a problem for many patients even nowadays; it occurs in up to 80% of cases and is identified during patient evaluation prior to the surgical event¹⁻³, where the main associated factors are the type of surgery, previous anesthetic experience, fear of pain, and fear of the unknown⁴⁻⁶. Benzodiazepines are effective anxiolytics, but are often accompanied by a not always desired sedation, as well as opiates, the side effects of which generate post-anesthetic care unit prolonged stays. All this has caused for many anesthesiologists to refrain from administering drugs for reducing anxiety and to start the anesthetic-surgical procedure with an anxious patient⁵.

Anxiety is a transient and situational emotional state that involves an intensified activation of the autonomic nervous system in response to a potentially harming event^{7,8}. It negatively impacts on surgery and anesthesia⁹, manifesting itself as a series of variable somatic symptoms such as sweating, palpitations, chest tightness, fatigue, frequent urination, headache, myalgia, insomnia, or digestive discomfort¹⁰, in addition to being often associated with post-operative pain, thus increasing analgesic requirements¹¹, which can lead to patient prolonged hospitalization and dissatisfaction¹².

The anesthetic concept of premedication was initially developed to prevent general anesthesia adverse effects when ether and chloroform were inhaled in the 1950s¹³. Various strategies are currently used to suppress pre-operative anxiety, including both pharmacological and non-pharmacological measures, which have been shown to be effective^{9,10}.

Among the pharmacological measures, as previously mentioned, benzodiazepines, narcotic analgesics, and anxiolytics are the most widely used, but none of them is free of adverse effects¹⁴. For this reason, pregabalin has been proposed as a potential option. Pregabalin is a structural analog of the inhibitory neurotransmitter gamma aminobutyric acid with anticonvulsant, anti-hyperalgesic, and anxiolytic properties¹⁵, which has also been shown to have dose-dependent analgesic efficacy, as well as to improve sleep quality and quality of life in general¹⁵. Its benefits in the management of pre-operative anxiety have only been demonstrated with doses higher than 150 mg, whereby dizziness is generated, which dismisses its use, with the 75-mg dose appearing to be inconclusive^{16,17}.

It is of great relevance for the properties of various doses to be tested to establish their efficacy and safety as a pre-operative anxiolytic drug; therefore, in this placebo-controlled study, our purpose was to demonstrate that, with a single 75-mg oral dose of pregabalin, the required anxiolytic effect can be achieved and the degree of pre-operative anxiety be decreased, as well as patient dizziness be reduced or avoided.

Methods

After authorization by the Local Research and Ethics Committee of our center, with approval number HAL 271, and once informed consent of each included patient was obtained, a randomized, double-blind, and controlled clinical trial was carried out.

The study took place from March 2017 to March 2018. A total of 100 adult patients who were scheduled for plastic surgery were considered for the performance of this study and were included in final statistical analysis.

The inclusion criteria were: adult patients older than 18 years of age, of either gender, American Society of Anesthesiologists (ASA) functional Class I or II, undergoing scheduled plastic surgery (blepharoplasty, rhinoplasty/rhinoseptumplasty, augmentation mammoplasty, mastopexy, liposuction, and rhytidectomy). Patients who refused to participate in the study, those allergic to the study drug, pregnant women, breastfeeding women, patients on treatment with benzodiazepines, anxiolytics, antidepressants or anticonvulsants, patients with psychiatric disorders, alcoholism, or drug addiction within previous 6 months, and those with a diagnosis of migraine were excluded from the study.

The sample size by difference of means¹⁸ considered a 95% confidence level and 90% power; for a difference of 1.2 anxiety points to be found on the visual analog scale for anxiety (VAS-A), at least 38 patients per group were required, plus 20% for potential losses; therefore, including at least 46 patients per group was planned, for a total sample of 92, with sampling being rounded to up to a practical total of 100 patients.

Randomization was carried out with the validated Random Allocation Software program, version 2.0, whereby two groups were derived.

One person who was unconnected to the study prepared the capsules with the same characteristics (one group with 75 mg of pregabalin and another with placebo), as well as opaque sealed envelopes with the randomization order, which were not opened until

patient inclusion in the study, and which contained the test for anxiety to be evaluated and the capsule (drug or placebo) the patient was to be administered.

Registration of the patients included in the study was carried out by a first observer at patient room, and the VAS-A was applied at that moment in order for the level of baseline anxiety to be assessed (Fig. 1).

A nurse administered the capsule 70 min before surgery according to the assignment in the envelope. After administration of the drug, blinding was maintained for the patient and the anesthesiologist in charge of the procedure. The information collector, in this case the nurse who cared for the patient, remained blinded to the received intervention all the time.

In the pre-operative area, just before admission to the operating room (70 min after having ingested the capsule), an anesthesiology resident applied the VAS-A to each patient again.

The results of all three observers were independently recorded, and by the end of the study, the records of both observers were analyzed by a third researcher, who completed the database and remained unconnected to the study. Finally, statistical analysis was carried out by a fourth subject, also unconnected to the study.

Descriptive analysis of independent variables was carried out using classic central tendency measures. For quantitative variables, the mean and standard deviation were obtained, and for qualitative variables, frequency, and percentage. Subsequently, whether the study variables of each group followed a normal distribution were investigated using the Kolmogorov–Smirnov test. To look for statistically significant differences between groups ($p < 0.05$), parametric tests (Student's t-test and Chi-square test) were used. When the groups were observed to be comparable, inferential analysis of the obtained data was carried out.

The search for differences between the control and the experimental group on anxiety scores was carried out taking into account VAS-A scores absolute value through analysis using Student's parametric t-test, with the SPSS program (IBM, version 19) and, finally, relative risk calculation with its 95% confidence interval for dependent variables (presence of adverse effects) was carried out as an extra analysis.

Results

One hundred patients were analyzed and there were no significant differences between both groups

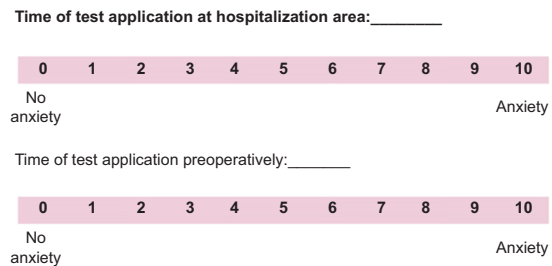


Figure 1. Visual analog scale for anxiety.

with regard to age, gender, weight, height, ASA physical status, and time intervals between drug administration and tests' application. Mean age in the placebo (PI) group was 39.28 years, while that in the pregabalin (Pg) group was 37.42 years. PI group average height was 1.63 cm, whereas that in Pg group was 1.64 cm. Weight had an equal distribution, with an mean of 63.62 kg in PI group and 63.14 kg in Pg group (Table 1). Gender was mostly female (87%), with a minority of male patients (13%), distributed in such a way that frequencies were equal and the proportion of female gender was similar (Pg = 44% vs. PI = 43%).

Once baseline VAS-A test was carried out, the number of minutes elapsed from blinded treatment administration to pre-operative VAS-A evaluation was similar in both groups (Pg = 72.3 ± 3.8 min vs. PI = 72.3 ± 5.0 min).

Baseline VAS-A score (at hospital admission) showed an overall mean of 4.6 ± 1.9 points and was significantly higher in the Pg group (Pg = 5.2 ± 2.1 points vs. PI = 4.1 ± 1.6 points; $p = 0.0035$). Subsequently, overall score for VAS-A second pre-operative application (70 min after taking the capsule) was 3.9 ± 2.1 points and was significantly lower in the Pg group (Pg = 3.2 ± 1.6 points vs. PI = 4.6 ± 2.3 points; $p = 0.0006$).

Given that data on this variable showed disparity of variances ($p = 0.0141$) or abnormal distribution, the Satterthwaite test was used to calculate the difference and was confirmed with nonparametric Mann–Whitney's U-test ($p = 0.0011$). The Pg group showed larger changes between both VAS-A assessments (Pg = -2.0 points vs. PI = 0.5 points) (Table 2).

After the results were analyzed, significant differences were observed in the first measurement of the degree of anxiety, with the level of baseline anxiety being higher in the Pg group, with a sample difference

Table 1. Comparison of anthropometric variables by group

	Group	N	Mean	T	p
Age (years)	Placebo	50	39.28	0.673	0.502
	Pregabalin	50	37.42	0.673	0.502
Weight (kg)	Placebo	50	63.62	0.215	0.830
	Pregabalin	50	63.14	0.215	0.830
Height (m)	Placebo	50	1.63	0.736	0.464
	Pregabalin	50	1.64	0.736	0.464

Table 2. Anxiety evaluations in the intervention groups

Evaluation	Pregabalin (n = 50)	Placebo (n = 50)	p*
Baseline VAS-A at hospitalization area (points)	5.2 ± 2.1	4.1 ± 1.6	0.0035
Preoperative VAS-A (points)	3.2 ± 1.6	4.6 ± 2.3	0.0006

VAS-A: visual analog scale for anxiety.

Mean ± standard deviation are indicated.

*Student's t-test.

of 1.12 points on VAS-A, in terms of absolute numbers (Table 3).

Discussion

So far, the search persists for an appropriate drug for anesthetic premedication that decreases pre-operative anxiety levels, and whose administration does not require permanent monitoring for side effects that compromise patient safety^{2,3}. On the other hand, post-operative dissatisfaction in plastic surgery is directly related to higher levels of anxiety¹⁹. Some authors have suggested that premedication for treating pre-operative anxiety in patients undergoing plastic surgery procedures should become a systematic practice, and that it should involve psychological and pharmacological support^{20,21}.

Oral pregabalin appears to be a good candidate for this purpose, given its relatively higher pharmacological safety profile in comparison with that of other drugs¹⁵. It modulates the release of excitatory neurotransmitters in hyperexcited neurons, its oral bioavailability is 90% and dose-independent, its pharmacokinetics are

Table 3. Comparison of VASA-measured anxiety

	Group	Mean	SD	Mann-Whitney's U-test	p
VAS-A at hospitalization area (anxiety)	Placebo	4.06	1.646	802	0.02
	Pregabalin	5.18	2.077		
Preoperative VAS-A (anxiety)	Placebo	4.56	2.278	781	0.001
	Pregabalin	3.16	1.595		

SD, standard deviation; VAS-A: visual analog scale for anxiety.

linear and predictable, inter-subject variability is low, and it does not bind to plasma proteins and easily crosses the blood-brain barrier¹⁵.

Different pregabalin doses have been studied in the literature for other indications, such as neuropathic pain and epilepsy, and the recommended starting dose is 150 mg/day divided into two to three doses, with dosage increasing to 300 mg/day within 1 week, with a maximum recommended dose of 600 mg/day^{22,23}.

For its use in pre-operative anxiety treatment, studied doses range from 75 to 300 mg, and according to this, a relationship with more side effects at higher doses and an inverse relationship with lower doses have been observed²⁴. As best evidence, there are some meta-analyses, in which efficacy of the use of pregabalin in the treatment of pre-operative anxiety is analyzed^{25,26}.

White et al.^{16,17} carried out a study to assess the efficacy of different pregabalin doses (75, 150 and 300 mg) as premedication for pre-operative anxiety in patients undergoing elective general surgery, as well as to measure sedation levels with each dose, and observed a significant increase in the level of sedation starting at 300 mg in outpatients both pre-surgically and post-surgically, but they failed to demonstrate a significant difference in anxiety reduction in the different groups.

The inconsistent finding regarding pregabalin ability to preoperatively reduce the level of anxiety may be related to a variety of factors, including the scales anxiety is evaluated with and the type of procedures pregabalin has been studied in. It should be noted that all studies that have previously shown that pregabalin reduces pre-operative anxiety have been in patients undergoing general, orthopedic, gynecological, neurological, and dental surgery, but not plastic surgery²⁷⁻³⁵. Patients scheduled for plastic surgery have high expectations for surgical results, as well as high levels of anxiety³⁶. In our study, the VAS-A was used,

which is a scale that has been validated and is one of the most widely used for this type of studies³⁷, which allowed us to demonstrate that the patient was anxious at hospital arrival, and this, in turn, allowed us to evaluate pregabalin 75 mg anxiolytic effect. We found that baseline assessment of the degree of anxiety (baseline VAS-A) was higher in the Pg group by 1 point in comparison with the Pl group, which denoted an apparent disadvantage for the active drug only by chance on treatment assignment; however, pre-operative VAS-A evaluation (second measurement) showed that the balance tipped in favor of pregabalin with almost 1.5 points less than in the placebo group. On both evaluations, the difference between groups was statistically significant, clearly showing that 70 min after premedication, there was a decrease in the degree of anxiety of approximately two points on the scale with pregabalin 75 mg versus a slight increase of 0.5 points on VAS-A with placebo within the same period.

On the other hand, Cegin et al.¹⁷ conducted a study using doses of 75, 150, and 300 mg, and a control group, to observe the effects of pregabalin when administered to patients before performing an infraclavicular block to assess the quality of the block, post-operative pain, and anxiolysis. The authors used the Ramsay sedation scale to assess patient anxiety and sedation. Ramsay scale values in the groups that were medicated with pregabalin 150 and 300 mg were higher in comparison with the other groups, and although the difference was not significant, a dose of pregabalin of 150 mg provided sufficient sedation to decrease peripheral oxygen saturation and, thereby, anxiety, with an inconsistent finding being reported with regard to the 75 mg dose.

However, our study suggests that a single 75-mg pregabalin dose is efficacious for reducing pre-operative anxiety, and when baseline characteristics of our population are observed, no significant differences were found between groups; for this reason, we highlight the strength of the study with regard to the comparable distribution of these characteristics between the intervention groups.

Our results are consistent with these studies that demonstrate and suggest that pregabalin is efficacious for the management of pre-operative anxiety. On the other hand, the report of side effects in our study was limited to sleepiness (somnolence) and dizziness: pregabalin produced somnolence and dizziness together in 44% of patients, somnolence in 16%, and dizziness in 2%. Dosage in one pregabalin 75 mg

administration had a lower rate of effects than those reported in the literature, which correspond to 22–38% for dizziness and 11–25%^{37,38} for somnolence. In addition, various adverse effects were not reported due to the rather short exposure period, including dry mouth, blurred vision, peripheral edema, weight gain, or others associated with prolonged treatment³⁹.

Conclusion

For all the above, we propose that pre-operative anxiety represents a symptom that should be treated with anxiolytic premedication in all patients. The results of this study are consistent and provide evidence that pregabalin is safe and effective for pre-operative anxiety control, and the 75-mg single dose appears to cover this need.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols or their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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