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REPORTS OF ORIGINAL INVESTIGATIONS

Preoperative pregabalin does not reduce propofol ED_{50}: a randomized controlled trial

La prégabaline en préopératoire ne réduit pas la DE_{50} du propofol: une étude randomisée contrôlée

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Abstract

Background *In many studies, gabapentinoids, such as pregabalin, have been shown to reduce preoperative anxiety. This anxiolysis is often accompanied by sedation, one of the most frequent side effects of pregabalin. We hypothesized that pregabalin taken preoperatively could reduce propofol requirements for induction of general anesthesia.*

Methods *A randomized double-blind placebo-controlled trial was conducted after approval by the local ethics committee. Fifty women aged 18-40 yr, American Anesthesiologists Society physical status I and II, and scheduled to undergo elective laparoscopic gynecologic procedures were enrolled after written consent. Treatment group patients were given pregabalin 150 mg po one hour before surgery while patients in the control group received a placebo. The primary outcome was the propofol dose required to achieve a targeted anesthetic depth in 50% of the population, i.e., effective dose $(ED)_{50}$. The ED_{50} was estimated using Dixon's up-and-down methodology. The targeted anesthetic depth was defined based on predetermined entropy monitoring values (State Entropy [SE] < 50 and Response Entropy [RE]-SE < 10). As a secondary outcome, we tested if pregabalin reduced pre-induction anxiety levels which were measured on a 0-100 scale.*

Results *The propofol ED_{50} was not statistically different between the pregabalin group (mean 1.33 $mg{\cdot}kg^{-1}$; 95% confidence interval [CI] 1.23 to 1.43) vs the placebo group (mean 1.37 $mg{\cdot}kg^{-1}$; 95% CI 1.28 to 1.46); P = 0.19. Also, pre-induction anxiety level was not different between groups (median 31; interquartile range [IQR] [10-52] vs median 42; IQR [4-71], respectively; P = 0.41).*

Conclusions *Preoperative pregabalin does not reduce propofol requirements in a population of healthy young women undergoing laparoscopic gynecologic procedures. This study failed to show a pre-induction anxiolytic effect of pregabalin in such a population. This trial was registered at www.clinicaltrials.gov (NCT01158859).*

Résumé

Contexte *Dans de nombreuses études, il a été démontré que les gabapentinoïdes tels que la prégabaline réduisaient l'anxiété préopératoire. Cette anxiolyse s'accompagne souvent de sédation, l'un des effets secondaires les plus fréquents de la prégabaline. Nous avons émis l'hypothèse que la prégabaline, prise avant l'opération, réduirait les besoins en propofol pour l'induction de l'anesthésie générale.*

Méthode *Une étude randomisée à double insu et contrôlée par placebo a été réalisée après avoir obtenu le consentement du comité d'éthique local. Cinquante femmes âgées de 18 à 40 ans, de statut physique I et II selon la classification de l'American Society of Anesthesiologists (ASA), et devant*

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Author contributions
François Moreau-Bussière and *Étienne de Médicis* contributed to the study design. *François Moreau-Bussière, Véronique Gagnon,* and *Étienne de Médicis* conducted the study, *François Moreau-Bussière* and *Véronique Gagnon* collected the data. *François Moreau-Bussière, Jonathan Gaulin, Yanick Sansoucy,* and *Étienne de Médicis* contributed to the data analysis and manuscript preparation. *Étienne de Médicis* is the archival author.

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subir des interventions gynécologiques non urgentes par laparoscopie, ont été recrutées après un consentement écrit. Les patientes du groupe traitement ont reçu de la prégabaline 150 mg po une heure avant la chirurgie, alors que les patientes du groupe témoin ont reçu un placebo. Le critère d'évaluation principal était la dose de propofol nécessaire pour atteindre une profondeur ciblée de l'anesthésie chez 50 % de la population, soit une dose efficace $(DE)_{50}$. La DE_{50} a été estimée à l'aide de la méthode dite up-and-down de Dixon. La profondeur cible a été définie sur la base de valeurs de monitorage d'entropie prédéterminées (entropie d'état [SE] < 50 et entropie de réponse [RE]-SE < 10). Pour notre critère d'évaluation secondaire, nous avons vérifié si la prégabaline réduisait les niveaux d'anxiété avant l'induction, mesurés sur une échelle de 0 à 100.

Résultats *La DE_{50} de propofol n'était pas différente d'un point de vue statistique entre le groupe prégabaline (moyenne 1,33 $mg{\cdot}kg^{-1}$; intervalle de confiance [IC] 95 % 1,23 à 1,43) et le groupe placebo (moyenne 1,37 $mg{\cdot}kg^{-1}$; IC 95 % 1,28 à 1,46); P = 0,19. De plus, le niveau d'anxiété pré-induction n'était pas différent entre les groupes (médiane 31; écart interquartile [EIQ] [10-52] vs. médiane 42; EIQ [4-71], respectivement; P = 0,41).*

Conclusion *La prégabaline en préopératoire ne réduit pas les besoins en propofol dans une population de jeunes femmes en bonne santé subissant des interventions gynécologiques par laparoscopie. Cette étude n'a pas montré d'effet anxiolytique pré-induction de la prégabaline dans une telle population. Cette étude a été enregistrée au www.clinicaltrials.gov (NCT01158859).*

Pregabalin, a drug classified as a gabapentinoid, was officially approved in Canada in 2005 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. More recently, it has gained approbation for management of pain associated with spinal cord injury and fibromyalgia.[A] In other countries, it is also used to treat partial onset epilepsy in adults and generalized anxiety disorder.[1]

Pregabalin's pharmacology, structure and mechanism of action have been reviewed in many articles.[1-4] Pregabalin is known to exert antiepileptic, analgesic, and anxiolytic effects, with the latter two of interest within the scope of anesthesia practice. The use of pregabalin in anesthesia is growing. In 2011, two meta-analyses were published on perioperative pregabalin administration for postoperative acute pain management.[5,6] Both studies showed an analgesic effect of perioperative pregabalin administration, as evidenced by a reduction in postoperative opioid or supplementary analgesic consumption. In addition, some studies found reduced anxiety following preoperative pregabalin administration *vs* placebo.[7-9] Of importance, this anxiolytic effect is often accompanied by somnolence or drowsiness, which is among the most frequent side effects of pregabalin.[9,10]

Consequently, considering the usual potentiation between sedatives and anxiolytics used in anesthesia, we hypothesized that pregabalin could reduce propofol requirements at induction of general anesthesia. Therefore, the primary aim of this study was to evaluate the impact of preoperatively administered pregabalin on the propofol dose needed to produce a targeted anesthetic depth. Knowledge of this interaction, if present, could prevent administration of an overdose of propofol in patients taking pregabalin. As a secondary outcome, we tested whether pregabalin reduces pre-induction anxiety levels.

Methods

Study design

We designed a randomized double-blind placebo-controlled trial for which we obtained local ethics board approval on March 18, 2009. The trial was carried out from April 2010 to August 2011 at the University of Sherbrooke teaching hospital. It was registered in July 2010 at www.clinicaltrials.gov (NCT01158859). We also obtained approval from Health Canada for the off-label use of pregabalin.

Outcomes and groups

The primary outcome was to evaluate the impact of preoperatively administered pregabalin on propofol requirements upon induction of general anesthesia. To fulfil this objective, we determined the propofol effective dose 50 (ED_{50}) to achieve a targeted anesthetic depth and compared the ED_{50} between a pregabalin group *vs* a placebo group. The up-and-down methodology (UDM) was used to calculate the ED_{50}.[11,12] We needed a binary (yes or no) response variable, inherent in dose-response relationships and UDM, and we used an entropy monitor (M-Entropy, GE Healthcare, Little Chalfont, UK) to quantify anesthetic depth as the variable. Entropy monitors are designed with two probes that are placed on the patient's forehead to acquire and process electroencephalographic (EEG) and frontal electromyographic (EMG) signals. The entropy monitor evaluates anesthetic depth by combining a State Entropy (SE) parameter (reflecting EEG activity) with a Response Entropy (RE)

[A] Pfizer Canada Inc. Product monograph: LYRICA (Pregabalin capsules). 2010: 1-60.

parameter (reflecting both EEG and frontal EMG activities). We defined a positive response as attainment of our targeted anesthetic depth, i.e., SE < 50 and RE-SE < 10. In the literature, these values are associated with clinically meaningful general anesthesia and a low probability of consciousness.[13-15] A negative response was defined as non-attainment of these values.

The secondary study outcome was pre-induction anxiety. To determine this result, we recorded patients' anxiety in the operating room immediately before induction using a visual analogue scale from 0-100.

Population and sample size

Our study population consisted of women aged 18-40 yr with American Society of Anesthesiologists physical status I or II and a body mass index (BMI) of 18-30 $kg \cdot m^{-2}$. They were scheduled to undergo elective short (less than three hours) laparoscopic gynecologic procedures under general anesthesia. Exclusion criteria included allergy to pregabalin or gabapentin; use of gabapentin, pregabalin, benzodiazepines, or antidepressants on a regular basis; chronic renal failure (renal clearance < 50 $mL \cdot min^{-1}$ estimated with the Cockcroft-Gault formula); alcohol or drug abuse; chronic use of analgesics other than acetaminophen or nonsteroidal anti-inflammatory drugs; known central neurological deficiency; suspected difficult intubation or mask ventilation; and known atypical pseudocholinesterase activity.

Based on two previous studies, we estimated the actual (standard deviation) propofol ED_{50} to be 1.4 (0.4) $mg \cdot kg^{-1}$,[16,17] and we considered a 25% decrease in the propofol induction dose to be clinically relevant. With an alpha error of 5% and a power of 80%, a sample size calculation using a two-sided Student's *t* test showed that 22 patients would be required in each group. Taking into account a 15% drop-out rate, we decided to include 25 patients per group, for a total of 50 patients.

Conduct of study

Written informed consent was obtained from all patients. The day before surgery, the patients were randomly allocated into five blocks of ten patients via computer-generated randomization tables. After randomization, a pharmacy technician (not involved in the study) prepared the appropriate medication tablet. Patients in the pregabalin group received a 150 mg tablet of the drug, while patients in the placebo group received a sugar tablet. The tablets were coated with opaque gelatin capsules to ensure uniform appearance, texture, color, and taste. An hour before surgery, a research assistant administered the coated pregabalin or placebo tablet and recorded baseline anxiety levels. In the operating room, the attending anesthesiologist or resident inserted an intravenous cannula and applied standard monitoring. Next, entropy probes were placed on the patient's forehead and the electrical impedance of the system was verified. At this moment, the patient's pre-induction anxiety level was recorded in addition to baseline SE and RE values. This assessment was performed by asking the patient to rate her anxiety level on a 0-100 scale, 0 meaning no anxiety at all and 100 the maximum level imaginable. After preoxygenation with a face mask, induction of general anesthesia was carried out. Gentle airway maneuvers or ventilation to prevent a decrease in arterial oxygen saturation were permitted. First, lidocaine 40 mg *iv* was administered to decrease propofol injection pain. Then, in a standardized fashion, the predetermined propofol dose was administered over one minute using a volumetric infusion pump. No other medication was allowed until completion of data collection. Between one and three minutes post-induction, we recorded the lowest SE and RE values displayed. These values were used to ascertain the targeted anesthetic depth. Three minutes post-induction marked the end of the study. Next, the attending anesthesiologist completed induction at his convenience and surgery proceeded. Throughout the entire study period, only the research assistant knew the dose and response of previous patients and was the only person preparing propofol infusions (blindly). Patients were known to belong to group 0 or 1, but the identification of those groups was unknown. The attending anesthesiologists and residents were unaware of the dose sequence and patient group.

The first patient in both groups received an induction dose of propofol 1.4 $mg \cdot kg^{-1}$ given over one minute. We chose this starting dose based on previous estimates of the propofol induction dose.[16,17] The next patient's dose was adjusted by a fixed value (step value) depending on the preceding patient's response. A positive response (the target anesthetic depth was reached) implied a decreased dose, and a negative response implied an increased dose for the next patient. The step value was set at 0.2 $mg \cdot kg^{-1}$, which is the standard deviation of the starting dose mentioned above.[17] This up-and-down dose variation sequence proceeded independently in both groups for the planned 25 subjects (no stopping rule was used).

Statistical analyses

Demographic and baseline characteristic variables were compared with the Mann-Whitney U test since variables were not normally distributed. The pre-induction anxiety levels (secondary outcome) were also compared with the

Mann-Whitney U test. For the primary outcome, we used the truncated version of the Dixon and Mood estimator to calculate the propofol ED_{50} and compared the results with a Student's t test.[11,12] Statistical significance was set at $P < 0.05$ for all analyses.

Results

Twenty-five women were randomized into each group. Four patients (three in the placebo group and one in the pregabalin group) were excluded from the study; therefore, data from the remaining 46 patients were included for analysis (Fig. 1). Demographic and baseline characteristics were comparable in both groups (Table 1). Baseline anxiety levels and median time from premedication to induction were similar. Baseline (standard deviation) entropy readings in the placebo group (SE 88 ± 1; RE 98 ± 1) and pregabalin groups were also similar [SE 88 (1); RE 98 (1) and SE 88 (1); RE 97 (1), respectively]. Fig. 2 depicts the propofol dose variation from patient to patient for each study group.

We found no statistically significant difference in propofol ED_{50} between the pregabalin group and the placebo group (Table 2). Minimal entropy values were reached before two minutes post-induction in 80% (20/25) of the patients who had a positive response (SE < 50 and RE-SE < 10). Every patient reached their minimal SE value before the three-minute mark, and entropy values were always increasing at that time. There was also no difference in pre-induction anxiety levels, with low median values in both groups (Table 2).

Discussion

The primary objective of this study was to evaluate the impact of preoperatively administered pregabalin on the dose of propofol needed to achieve a targeted anesthetic depth. Our results suggest that preoperative administration of pregabalin has no impact on the propofol dose-response relationship. This is evidenced by a propofol ED_{50} that is similar in the pregabalin and placebo groups.

There could be many explanations for the absence of a propofol-sparing effect using a single preoperative dose of pregabalin. One possible explanation could be the difference in target receptors between pregabalin and propofol. Propofol is a gamma-aminobutyric acid $(GABA)_A$ receptor agonist that produces general anesthesia. On the other hand, the action of pregabalin is totally independent from GABA-related mechanisms. It acts by binding to the alpha-2-delta subunit of presynaptic neuronal voltage-gated calcium channels.[2] This difference in mechanism of action could explain the absence of additive or synergistic sedative effects between the two drugs.

The validity of our results is supported by the randomized double-blind placebo-controlled design of our study. In addition, the study groups were comparable with respect to factors that could have influenced either propofol tolerance (age) or pharmacokinetics (BMI). Concerning time from premedication to induction, our results show that patients received pregabalin around one hour or more before induction in both groups, and pregabalin peak plasma levels are known to be reached about one hour after oral administration. Therefore, even if the pregabalin group received the drug 25 minutes earlier than the placebo group

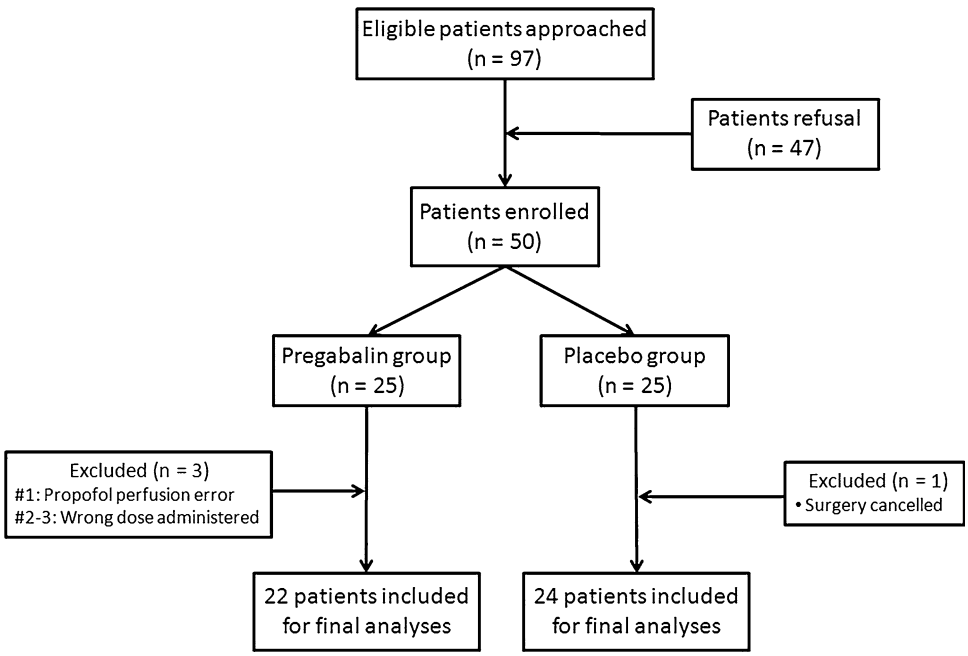

Fig. 1 Study flow diagram

Table 1 Demographic and baseline values by group

	Placebo group ($n = 22$)	Pregabalin group ($n = 24$)
Age (yr)	33 [29-36]	36 [31-38]
Body mass index ($kg \cdot m^{-2}$)	24 [21-27]	25 [21-27]
Time from premedication to induction (min)	65 [51-87]	90 [62-110]
Baseline anxiety level (on a 0-100 scale)	30 [3-66]	32 [23-55]

Values are shown as median [interquartile range]

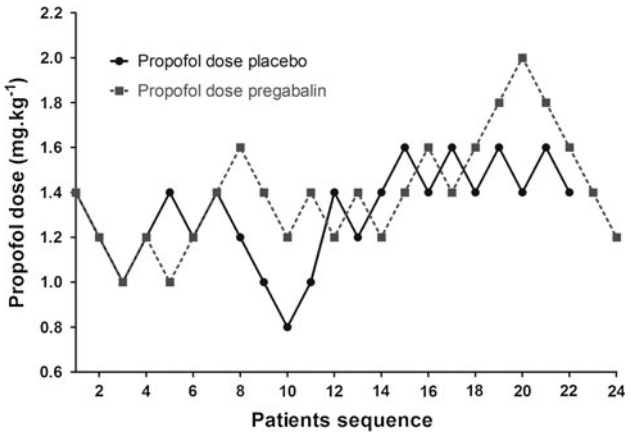

Fig. 2 Propofol dose in both groups. An up-and-down methodology was used; each patient's dose was based on the previous patient's response. The starting dose was 1.4 $mg \cdot kg^{-1}$ and changed by increments or decrements of 0.2 $mg \cdot kg^{-1}$

Table 2 Primary and secondary outcomes

	Placebo group ($n = 22$)	Pregabalin group ($n = 24$)	*P* value
Propofol ED_{50} ($mg \cdot kg^{-1}$)	1.37 (1.23 to 1.43)	1.33 (1.28 to 1.46)	0.19
Pre-induction anxiety level (on a 0-100 scale)	42 [4-71]	31 [10-52]	0.41

Values are shown as ED_{50} (95% confidence interval) and median [interquartile range]. ED_{50} = effective dose 50

(statistically not significant), we consider this difference to have no impact on the results; the crucial point is that at least one hour elapsed after premedication. Pregabalin's bioavailability exceeds 90% and it is dose-independent, making it suitable for single high-dose preoperative administration.[3] In fact, pregabalin 150 mg *po* used as a single dose in this study is the approximate equivalent of gabapentin 900 mg *po*, which exceeds the maximum absorbable single dose of this drug. This is one reason why we chose to use pregabalin instead of gabapentin, which has a lower bioavailability at high doses and reaches peak plasma levels three times more slowly.[18] We therefore consider this dose sufficient to show a clinically relevant interaction, if it existed. Finally, the statistical method used in the present study is robust. The UDM used to estimate propofol ED_{50} is well validated in the literature, and the truncated version of the Dixon and Mood estimator has been shown superior to other variants. Published literature also confirms that a sample size of 20 subjects is sufficient to obtain a valid estimate of an ED_{50} in most clinical scenarios.[12] This is supported by the fact that our ED_{50} values (ED_{50} 1.33 $mg \cdot kg^{-1}$; 95% CI 1.23 to 1.43 and ED_{50} 1.37 $mg \cdot kg^{-1}$; 95% CI 1.28 to 1.46) are in accordance with reference values found in the literature (ED_{50} 1.39 $mg \cdot kg^{-1}$; 95% CI 1.23 to 1.55 and ED_{50} 1.40 $mg \cdot kg^{-1}$; 95% CI 1.31 to 1.48).[16,17] A smaller reduction in propofol ED_{50} ($< 25\%$) by pregabalin premedication could exist and be missed by our study design, although we presume that it would not be clinically significant.

On the other hand, our study also has some limitations. First, in spite of a robust and valid methodology, our results are applicable to only a limited population of healthy young women. Second, although propofol perfusion was given in a standardized fashion over one minute, inter-patient variability in pharmacokinetics could affect propofol plasma levels and thus anesthetic depth. Nevertheless, our view is that randomization balanced pharmacokinetic differences in both groups, and if any differences remain, they are likely to be small and have a clinically irrelevant impact on the results. Third, the three-minute evaluation period after propofol induction could be considered too short; however, minimal entropy values were reached before the three-minute mark, confirming that the duration of the evaluation period was sufficient to record the maximal propofol effect in every patient. Also, relying on entropy monitoring technology to quantify anesthesia depth could be considered a weakness. Although bispectral index (BIS) monitoring is considered the gold standard among anesthesia depth monitors, we preferred to use entropy because it is less prone to plateau in the range of values close to general anesthesia and therefore is more suited to our study design.[14] Moreover, it adjusts as fast as BIS to changing depths of anesthesia.[19] Unfortunately, like most other anesthesia depth monitors, entropy has some pitfalls and is subject to artefacts.[20,21] To ensure valid measurements of anesthesia depth in our patients, we avoided use of artefact-inducing devices during the data collection period and used a single anesthetic agent (propofol). Indeed, anesthesia induced by GABA agonists is very well measured by entropy monitors. We also preferred to use an objective EEG end point over a clinical one (such as a sedation scale or similar measures) to reduce

inter-observational variability. In fact, due to the large number of anesthesiologists involved, clinical end points would be more prone to interpretations and bias. Finally, concern could be raised about interference between tablet coating and enteric absorption of pregabalin. In fact, the opaque gelatin capsules used in this trial dissolve rapidly and delay main compound absorption by about one minute, which is not clinically relevant.[22]

As a secondary outcome, we failed to show a reduction in pre-induction anxiety levels after pregabalin administration when we compared results using pregabalin *vs* placebo. This is contrary to the majority of recent studies[7-9] but in accordance with a study by White *et al*.[23] This study had low baseline anxiety levels similar to ours, and we consider this a plausible explanation for the lack of anxiolytic effect in our study. The low baseline anxiety values could be due to the relatively benign nature of the surgeries studied (e.g., tubal ligation, hysteroscopy). Indeed, it is hard to show a reduction in values that are already low at the outset. In contrast, most studies that showed a reduction in anxiety using pregabalin had relatively high baseline anxiety values.

In conclusion, in our randomized double-blind placebo-controlled trial in a population of young healthy women undergoing short laparoscopic gynecologic procedures, pregabalin 150 mg *po* administered one hour preoperatively made no impact on the dose of propofol ED_{50} required to achieve a targeted anesthetic depth. This finding suggests that no decrease in propofol induction dose is necessary following pregabalin premedication. Finally, we did not show a pre-induction anxiolytic effect of pregabalin in our study population.

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Conflicts of interests Étienne de Médicis was a site investigator for an international study on pregabalin sponsored by Pfizer.

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