Online version at http://www.minervamedica.it

Minerva Anestesiologica 2020 January;86(1):56-63
DOI: 10.23736/S0375-9393.19.13734-0

ORIGINAL ARTICLE

Role of preoperative pregabalin in reducing inhalational anesthetic requirements in abdominal hysterectomy: randomized controlled trial

Nesrine A. EL-REFAI [1] *, Jehan H. SHEHATA [1], Ahmed LOTFY [1], Ahmed M. ELBADAWY [1], Reham A. ABDEL RAHMAN [1], Tamer M. GAMALELDIN [1], Nasser M. DOBAL [1], Ahmed A. MOHAMED [1], Tahani A. FARRAG [1], Yaser M. SHAFIK [2], Adham F. KAMAL [3]

[1]Department of Anesthesia, Faculty of Medicine, Cairo University, Cairo, Egypt; [2]Department of Anesthesia, Egyptian Medical Military Academy, Cairo, Egypt; [3]Department of Anesthesia, Students' Educational Hospital, Cairo, Egypt

*Corresponding author: Nesrine A. El-Refai, Department of Anesthesia, Faculty of Medicine, Cairo University, 38 Yehia Ibrahim Street, Zamalek, Cairo, Egypt. E-mail: nesrinerefai@hotmail.com

ABSTRACT

BACKGROUND: Preoperative oral pregabalin controls postoperative pain and decreases anesthetic requirements in total intravenous anesthesia. In this study, we hypothesized that preoperative pregabalin reduces inhaled isoflurane requirements.

METHODS: We investigated the effectiveness of preoperative oral pregabalin 150 mg in women undergoing elective open total abdominal hysterectomy under general anesthesia. A prospective, randomized, double-blind, controlled study was conducted in a university hospital. The study included 50 women (18-60 yrs.), ASA I or II, admitted for abdominal hysterectomy under general anesthesia. Exclusion criteria were allergy to pregabalin; calcium channel blockers, antiepileptic drugs, antidepressant drugs, any analgesics, sedatives, or oral hypoglycemic agents. Patients were randomized into two groups; Pregabalin group received oral pregabalin 150 mg and placebo group. Main outcome measures was inhaled isoflurane requirements to maintain hemodynamics ±20% of baseline and bispectral index of 40 - 60, measured using MAQUET Flow-I anesthetic machine. Secondary outcomes were attenuation of pressor response to intubation, postoperative pain, and first time for rescue analgesia, total analgesics and adverse effects.

RESULTS: Isoflurane consumption was significantly less in pregabalin group (7.80±1.27 mL h -1) *versus* (12.27±2.49 mL h-1) in the control group, (P=0.00). Better hemodynamic stability was in pregabalin group. First postoperative hour: the mean VAS Score was significantly higher in control group (7.10±1.20) compared to pregabalin group (4.50±1.70), P<0.001. More dizziness was in pregabalin group.

CONCLUSIONS: Preoperative pregabalin 150 mg, 1 h before total abdominal hysterectomy has an inhaled anesthetic-sparing effect, maintain hemodynamics and optimizes postoperative analgesia.

(*Cite this article as:* El-Refai NA, Shehata JH, Lotfy A, Elbadawy AM, Abdel Rahman RA, Gamaleldin TM, *et al.* Role of preoperative pregabalin in reducing inhalational anesthetic requirements in abdominal hysterectomy: randomized controlled trial. Minerva Anestesiol 2020;86:56-63. DOI: 10.23736/S0375-9393.19.13734-0)

KEY WORDS: Pregabalin; Isoflurane; Anesthetics, inhalation; Surgery; Consciousness monitors; Hysterectomy.

Balanced anesthesia provides a mixture of sedatives, analgesics, and anesthetics to induce anesthesia using lower doses of each drug. A popular regimen usually includes the combination of the inhalational anesthetic as hypnotic agent and a short acting opioid.

Balanced anesthesia offers preoperative anxiolytic, perioperative analgesia, stable hemodynamics and minimal adverse effects. A popular regimen usually include the combination of a short acting opioid and minimal concentration of volatile anesthetics.[1]

Inhalation anesthetics inhibit excitatory neurotransmitters through direct presynaptic mecha-

nisms. Isoflurane is a potent inhibitor of glutamate release, the principal excitatory neurotransmitter in the central nervous system, as well as inhibiting the release of norepinephrine, dopamine, and acetylcholine.[2, 3]

Pregabalin is a structural analog of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), but it is not functionally related to it. Similar to its predecessor, gabapentin, it binds with high affinity to (α2δ) subunit of the presynaptic voltage-gated calcium channels reducing the release of calcium and subsequently inhibiting the release of excitatory neurotransmitters including glutamate, norepinephrine, substance P and calcitonin gene-related peptide thus increasing neuronal GABA level[4] and thereby preventing hyperalgesia and central sensitization.[5]

Pregabalin plays an established role in the management of neuropathic pain and other chronic pain neuralgia.[6] Pregablin has antiepileptic, analgesic, anxiolytic and sleeps modulating activities.[7] Preoperative pregabalin has been used in various doses and surgeries as a non-opioid adjuvant to control postoperative pain and limit reliance on opioid analgesia.[8-11]

Recently, administration of preoperative pregabalin in intravenous sedation[12] and total intravenous anesthesia[13] has decreased propofol dose needed to maintain adequate sedative and anesthetic levels.

Up to date, the effect of preoperative pregabalin on inhaled anesthetic depth is unknown.

The primary outcome of this study was inhaled isoflurane requirements (mL h^{-1}), needed to maintain intraoperative hemodynamic stability ±20% of baseline and bispectral index (BIS) value within 40-60, after pregabalin premedication. Secondary outcomes included attenuation of the pressor response to intubation and extubation, pain intensity postoperatively, first time to rescue analgesia and total pethidine consumption; and the incidence of adverse effects related to pregabalin including sedation, headache, blurred vision, dizziness, nausea and vomiting for 6h postoperatively.

Materials and methods

This study was approved by the institutional review board of Cairo University -Kasr AlAini (Research Ethics Committee). Approval Number: N- 67-2017. The study was registered at ClinicalTrails.gov (NCT 03302208).

This prospective, parallel, randomized, double-blind, placebo-controlled clinical study was performed in Cairo University Hospital, Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Cairo University, Egypt. Written informed consent was obtained from each patient.

Patients were enrolled from June to September 2017. Eligible participants were ASA physical status I or II women, aged between 18 and 60 years, who were admitted for elective open total abdominal hysterectomy surgery under general anesthesia. Exclusion criteria were allergy or hypersensitivity to pregabalin; patients on calcium channel blockers, antiepileptic drugs, antidepressant drugs, any analgesics or sedatives including Pregabalin, or oral hypoglycemic agents; and patients with severe cardiovascular, renal, hepatic or neurological dysfunction. Fifty patients were randomly assigned to one of two groups by using a computer-generated random number table (CONSORT flow chart shown in Figure 1). The control group (group C, N.=25) received oral placebo capsules containing fine sugar, pregabalin group (group P, N.=25) received oral pregabalin 150 mg (Lyrica TM, Pfizer Inc.) at 1 h before the anticipated time of the anesthetic induction. The placebo and pregabalin were provided in a white capsule by a pharmacist who was not otherwise involved in this study. The capsules were further packed in opaque plastic containers labeled with the randomization number. The medication was administered by anesthesiologists who also performed the subsequent assessments. Anesthesiologists and patients were not aware of the content of the capsules. The randomization was not revealed to the investigators before all measurements were conducted and entered into the database.

The night before surgery, the preoperative assessment was done and all patients were instructed on visual analog scale (VAS 0-10 cm) for assessment of pain (VAS 0= no pain, VAS 10= unbearable pain). Following 8 h period of fasting, the patients attended at the preanesthetic room where baseline hemodynamic measurements; systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and heart rate (HR) were

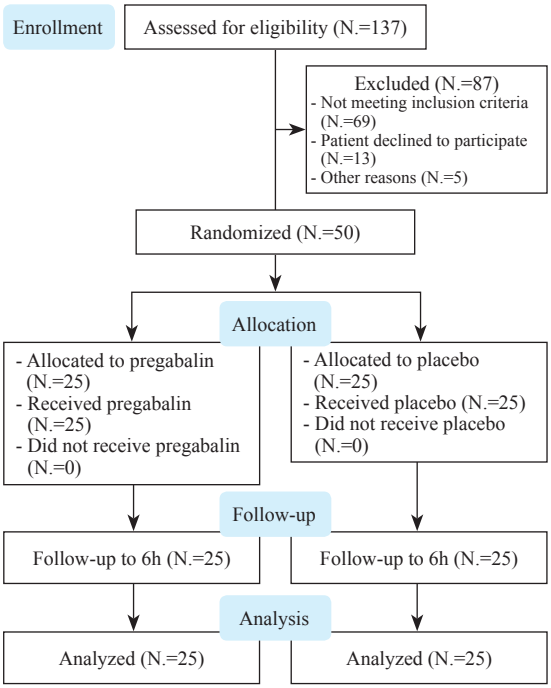

Figure 1.—CONSORT diagram of the study.

determined from the mean of three readings that fell within 10% of each other, taken at least one minute apart. Intravenous access was established with an 18-gauge peripheral intravenous catheter and all patients received ranitidine 50 mg IV and metoclopramide 10 mg IV. Patients were transferred to the operating room where standard monitoring including electrocardiography (ECG), pulse oximetry (SpO2), non-invasive blood pressure monitoring and Bi-Spectral Index monitor (Aspect Medical Systems Inc. Leiden, the Netherlands) were applied.

A standardized anesthesia protocol was followed. General anesthesia was induced with thiopental sodium 5-7 mg kg^{-1} IV, fentanyl 1 µg kg^{-1} IV and atracurium 0.5mg kg^{-1} IV. Laryngoscopy and intubation were done after three minutes. Patients' lungs were mechanically ventilated, using MAQUET Flow-I anesthetic machine (Model No. USE1903A. GE Medical Systems Information Technologies, Inc., Freiburg, Germany), a tidal volume of 6-8 mL kg-1, inspired oxygen fraction (FIO2) of 0.6 and the respiratory rate was adjusted to maintain normocapnia (end-tidal CO2 between 34-38 mmHg). All patients received intravenous lactated Ringer's solution based on a calculated preoperative deficit and estimated intraoperative blood loss. Isoflurane concentration was adjusted to maintain intraoperative hemodynamic stability (blood pressure and heart rate ±20% of baseline and BIS value in the range of 40-60). SBP, DBP, MBP and HR were recorded immediately after anesthetic induction, after intubation and after three minutes, five minutes, ten minutes and every 15 minutes until extubation. Hemodynamic parameters out of range±20% of baseline values in the presence of normocapnia were managed by an incremental increase or decrease of isoflurane till hemodynamic normalization. If no response after 10 minutes, additional doses of fentanyl 0.5 µg kg-1 were given. At the end of surgery, anesthesia was discontinued, surgical time was checked and recorded and residual muscle relaxant effects were reversed with neostigmine 0.04-0.08 mg kg^{-1} IV and atropine 0.01-0.02 mg Kg^{-1} IV. Intraoperative isoflurane requirement was calculated as mean value (mL h^{-1}) by dividing the total consumption (mL), measured using MAQUET Flow-I anesthetic machine, by the duration of surgery (h) to correct for the variable duration of surgery.

Postoperatively, hemodynamic measurements were recorded immediately after extubation, at three minutes and ten minutes. Postoperative pain was assessed using VAS and pethidine 1mg kg^{-1} Intramuscular was given as rescue analgesia for postoperative pain if VAS Score ≥6. The time to requirement of first rescue analgesic and total pethidine consumption in six hours postoperative were recorded. Postoperative nausea, vomiting, headache, dizziness, blurred vision and sedation which might occur as side effects of pregabalin were evaluated at one, two, four and six hours postoperatively. Over sedation was defined as a score ≤2 on a five-point scale.[14] Score one (barely arousable): Asleep, needs shaking or shouting to arise. Score two (asleep): Eyes closed, arousable with a soft voice or light touch. Score three (sleepy): eyes opened, less active, and responsive. Score four: awake. Score five: agitated.

Sample size

The number of patients required for the statistical analysis to identify a clinically relevant effect

of oral pregabalin on the primary endpoint; inhalation anesthetic requirement (inhaled isoflurane requirement) was calculated using Student's *t*-test. Taking a power of the study of 80% and an alpha error of 0.05, based on a previous study that showed preoperative pregabalin *versus* placebo reduced intraoperative inhalational anesthesia (Sevoflurane %) by 0.9 *versus* 1.2 with standard deviation (SD)±0.31, a minimum number of 20 patients were needed for each group. This number was increased to 25 patients per group to compensate for possible dropout.

Statistical analysis

Data were statistically described in terms of mean±standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Analysis of variance (ANOVA) for repeated measures was used to analyze data of blood pressure and heart rate. Comparison of quantitative variables between the study groups was done using the Student's *t*-test for independent samples. For comparing categorical data, χ^2 test was performed. The Fisher's Exact Test was used instead when the expected frequency was less than five. P values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

Results

Of 137 women who were assessed for eligibility, 50 patients completed the study as planned without dropouts (CONSORT Flow Chart, Figure 1). Patients' characteristics were comparable in both groups. There were no statistically significant differences between the two groups regarding age, weight, height and ASA physical status (Table I). While the mean surgical time was significantly less in pregabalin group (1.47±0.47 h) compared to the control group, where the mean surgical time was (2.04±0.48 h) (P value =0.00).

Isoflurane requirements were calculated as the mean value (mL h^{-1}) by dividing the total consumption (mL) of each patient by the duration of surgery (h). Pregabalin group consumed significantly less isoflurane during surgery (7.80±1.27 mL h-1) compared to the control group which consumed 12.27±2.49 mL h-1, P=0.00.

The baseline hemodynamic parameters were similar in both groups. Better intraoperative hemodynamic stability was observed in the pregabalin group compared to the control group; no significant changes in heart rate or blood pressure in pregabalin group. In the control group, the HR was significantly higher during the first 75 min of surgery and after extubation at three and ten minutes compared to pregabalin group (Figure 2, Table II). In the Control group, MBP was significantly higher compared to pregabalin group at five minutes after induction, throughout surgery; and at three and ten min after extubation (Figure 3, Table III).

Within the first hour, the mean VAS score in patients in the control group was significantly higher (7.1±1.2) compared to those in pregabalin group (4.5±1.7), (P <0.001) and all patients in the control group (25 patients) required postoperative pethidine/IM (66.00±23.81 mg). Only two patients in the pregabalin group needed pethidine I/M, one received 75 mg after two hours and the other received 50 mg after four hours, postoperatively. The incidence of side effects, postoperatively, were comparable in both groups (nausea, vomiting, headache, and blurred vision). However

TABLE I.—*Patients' characteristics and surgical time in pregabalin group (group P) and control group (group C).*

	Group (P) (N.=25)	Group (C) (N.=25)	P value
Age (year)	49.10±4.80	47.10±5.0	0.15
Weight (kg)	74.33±9.53	73.32±9.52	0.82
Height (cm)	166.32±7.20	165.41±7.70	0.61
ASA I/II (patients' number)	11/14	8/17	0.38
Surgical time (h)	1.47±0.47	2.04±0.48	0.000*

Data are presented as mean±SD or number and percentage (%).
*Statistically significant difference between the two groups.

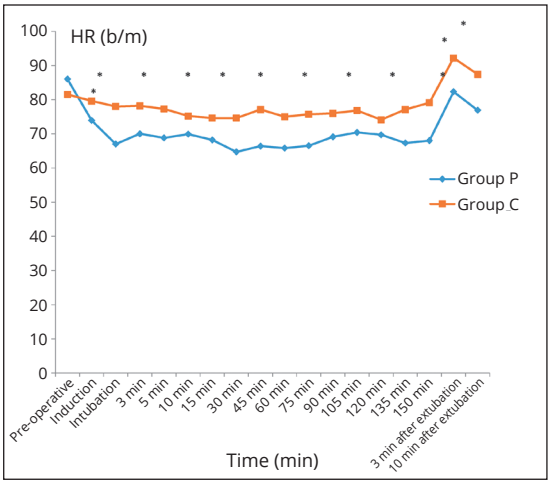

Figure 2.—Heart rate in the pregabalin group and control group.
*Statistically significant value.

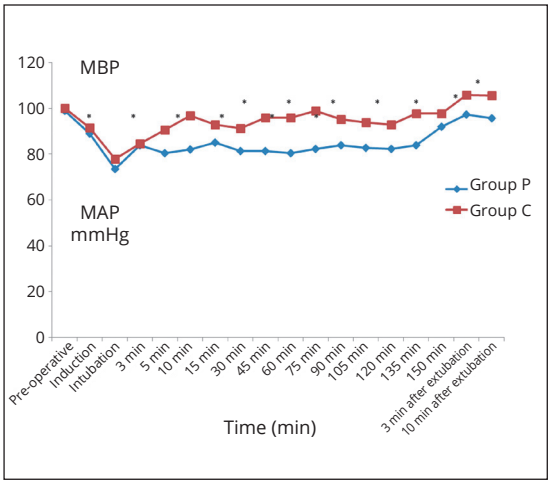

Figure 3.—Mean blood pressure in the pregabalin group and control group.
*Statistically significant value.

15 patients (60%) in the pregabalin group experienced dizziness compared to only two patients (8%) in the control group (P<0.001). Postoperatively, patients in the pregabalin group were less apprehensive and well sedated compared to those in the control group, who were awake and agitated.

Over sedation was defined as a score ≤2 on a 5-point scale. In the pregabalin group, 28% of patients had score one (barely arousable) only within the first hour postoperative. This is considered acceptable for sedation in the recovery room. None of our patients show any adverse effects of over sedation like hypoxia and none of them needed re-intubation.

Discussion

In this study, a single dose of oral pregabalin 150 mg one hour prior to anesthetic induction reduced intraoperative inhaled isoflurane requirement (≈36.4%) needed to achieve an adequate level of anesthesia while maintaining hemodynamic stability in ASA I and II women undergoing elective total abdominal hysterectomy under general anesthesia.

To the best of our knowledge isoflurane-sparing effect of preemptive pregabalin has not been demonstrated in previous studies. Recently, Gupta and Colleagues[14] compared the effect of two doses

TABLE II.—*Two-way analysis of variance with repeated measures heart rate changes over time.*

	Group P	Group C	P value (time)	P value (groups)	P value (interaction)
Preinduction HR*	86±11.7	81.5±11.4	<0.001	0.058	<0.001
Intra-operative HR	70.5±11.6	76.4±7.8			
Postoperative HR*	79.6±4.5	89.7±8.6			

*Significant difference.
HR: heart rate.

TABLE III.—*Two-way analysis of variance e repeated measures. Mean arterial pressure changes over time.*

	Group P	Group C	P value (time)	P value (groups)	P value (interaction)
Preinduction MAP	99±8.1	100±9.9	<0.001	<0.001	0.005
Intra-operative MAP	82.2±4.6	92.4±5.8			
Postoperative MAP	96.4±10.7	105.7±7.6			

MAP: mean arterial pressure.

of pregabalin premedication (75 mg night before surgery and either 150 mg or 300 mg one hour before surgery) with diazepam (10 mg night before surgery and 5mg one hour before surgery) on perioperative anesthetic and analgesic requirements during laparoscopic cholecystectomy. They demonstrated that pregabalin reduced the consumption of thiopentone, fentanyl and sevoflurane without significant differences between the two doses. They used sevoflurane concentration (%) which was needed constantly for more than 50% duration of surgery. Sevoflurane % was 1.20±0.30 in diazepam group, 0.93±0.25 in pregabalin 150mg group and 1.00±0.00 in pregabalin 300 mg group.

In our study, the actual total volume of isoflurane consumed by each patient was measured using MAQUET Flow-1 anesthetic machine and was used to calculate the mean isoflurane requirement. Pregabalin group consumed 7.80±1.27 mL h^{-1} while, the control group consumed 12.27±2.49 mL h^{-1}.

In addition, BIS value was recorded throughout surgery and maintained in the range of 40-60 to ensure an adequate level of anesthesia.

Preliminary investigation of preoperative pregabalin in total intravenous anesthesia patients[13] reported a decreased anesthetic requirement (required propofol and remifentanil doses) to obtain bispectral index value less than 60. The total amount of propofol was lower after premedication with pregabalin 300 mg compared to that after pregabalin 150 mg. Similarly, in intravenous sedation oral premedication with pregabalin (100 and 200 mg) reduced the amount required to obtain an acceptable and adequate sedation level.[12]

The mechanism by which pregabalin has an anesthetic-sparing effect has not been previously studied. The regulation of neurotransmitter release from presynaptic nerve terminals may be related to anesthetic action in the central nervous system.[13] Pregabalin inhibits the release of excitatory neurotransmitters from presynaptic terminals;[4] therefore, it is probably reasonable that pregabalin affects anesthetic action.[14]

In this study, oral pregabalin 150 mg given an hour prior to anesthetic induction produced fruitful anesthetic sparing effect, as pregabalin demonstrated highly predictable and linear pharmacokinetics. It has extensive and rapid absorption with maximum plasma concentrations attained within one hour and absolute bioavailability of approximately 90% irrespective of the dosage.

A single dose of oral pregabalin 150 mg was chosen, as it has been proven to be an optimal dose for postoperative pain management.[15, 16]Mishriky *et al.*[8] reported in a systematic review that a single preoperative dose was as effective as multiple doses and all doses of pregabalin (75, 100, 150 and 300) resulted in opioid-sparing effect. However, smaller doses (75, 100 mg) were less effective and higher doses (300 mg) were limited by adverse effect; mainly dizziness and somnolence.

Similar to that reported in previous studies in various patient populations undergoing different surgeries,[17-19] pregabalin premedication resulted in intraoperative hemodynamic stability with suppression of the reflex tachycardia and hypertension related to intubation and extubation. The mechanism by which pregabalin attenuates hemodynamic pressor response to laryngoscopy and intubation is unknown, however, as a calcium channel modulator[4] it may be attributed to inhibition of calcium efflux from muscle cells.[20]

Pregabalin as a preventive analgesic that attenuates neuronal hyperexcitability and central sensitization[5] resulted in remarkable pain relief with reduction of the narcotic requirement in the immediate postoperative period. This goes in accordance with plenty of studies that proved pregabalin's antinociceptive action in relieving postoperative pain.[8-11, 21-27] In addition, it prolonged the duration for first rescue analgesia up to six hours postoperatively. Prolongation of postoperative analgesia has been previously described.[21, 22, 26, 27] This favorable effect may be attributable to pregabalin's long elimination half-life (ranging from 5.5 to 6.7 h).[28]

A single dose of pregabalin 150 mg was generally well tolerated with limited side effects. The most commonly encountered side effects after pregabalin administration were dizziness and somnolence. Fifteen patients suffered from postoperative dizziness in the pregabalin group while only two patients had dizziness in the control group, this goes in accordance with results of previous studies[11, 21-27]

In the present study, though the incidence of postoperative nausea and vomiting (PONV) was

less in patients premedicated with pregabalin (20% and 8% respectively) compared to patients in the control group (44% and 20% respectively), the difference did not reach statistical significance. This result is consistent with that of some studies.[17, 21, 25] the potential antiemetic effect of pregabalin is not shown in our study as the incidence of PONV was a secondary endpoint; a larger study may be needed. However, other studies have verified the effectiveness of pregabalin in reducing PONV and rescue antiemetic in patients undergoing abdominal hysterectomy[29]and various other surgeries.[30] Gabapentinoids may preempt PONV directly through inhibition in the area postrema, mitigation of tachykinin neurotransmission and reduction in postoperative inflammation,[31] or indirectly as a product of perioperative opioid-sparing effect.[9]

The sedation observed in patients receiving pregabalin was modest and clinically acceptable. In intravenous sedation, pregabalin augments the sedative effect of propofol.[12, 32] In some studies, pregabalin has been used as preoperative premedication to increase perioperative sedation,[33, 34] while others reported the increased sedation level after pregabalin administration as a side effect.

Limitations of the study

These results are promising. However, this study is limited by its sample size, the homogeneity of the patient population and the exclusion criteria. Furthermore, we did not determine the potential antiemetic effect of pregabalin or the effect of sedation on patient's stay in the recovery room.

Further large studies in different patient populations are needed to verify the anesthetic-sparing effect of pregabalin and its long-term beneficial sequelae.

Conclusions

A single administration of pregabalin 150 mg, one hour before elective open total abdominal hysterectomy, was effective at reducing intraoperative isoflurane requirement, attenuating hemodynamic response to laryngoscopy, endotracheal intubation, and extubation, as well as optimizing the quality and duration of postoperative analgesia without clinically serious adverse effects. Thus, pregabalin may be a useful adjuvant to general anesthesia in selected patients.

What is known

• Preoperative oral pregabalin helps to control postoperative pain.

• Preoperative oral pregabalin was found to decrease anesthetic requirements in total intravenous anesthesia.

What is new

• Preoperative pregabalin 150 mg, one h before total abdominal hysterectomy has an inhaled anesthetic-sparing effect.

• Preoperative pregabalin maintains hemodynamics during major gynecological surgery.

• Preoperative pregabalin also optimizes postoperative analgesia.

References

1. Tonner PH. Balanced anaesthesia today. Best Pract Res Clin Anaesthesiol 2005;19:475–84.

2. Westphalen RI, Desai KM, Hemmings HC Jr. Presynaptic inhibition of the release of multiple major central nervous system neurotransmitter types by the inhaled anaesthetic isoflurane. Br J Anaesth 2013;110:592–9.

3. Baumgart JP, Zhou ZY, Hara M, Cook DC, Hoppa MB, Ryan TA, *et al.* Isoflurane inhibits synaptic vesicle exocytosis through reduced Ca2+ influx, not Ca2+-exocytosis coupling. Proc Natl Acad Sci USA 2015;112:11959–64.

4. Bauer CS, Rahman W, Tran-van-Minh A, Lujan R, Dickenson AH, Dolphin AC. The anti-allodynic alpha(2)delta ligand pregabalin inhibits the trafficking of the calcium channel alpha(2)delta-1 subunit to presynaptic terminals in vivo. Biochem Soc Trans 2010;38:525–8.

5. Bannister K, Sikandar S, Bauer CS, Dolphin AC, Porreca F, Dickenson AH. Pregabalin suppresses spinal neuronal hyperexcitability and visceral hypersensitivity in the absence of peripheral pathophysiology. Anesthesiology 2011;115:144–52.

6. Baidya DK, Agarwal A, Khanna P, Arora MK. Pregabalin in acute and chronic pain. J Anaesthesiol Clin Pharmacol 2011;27:307–14.

7. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 2007;29:26–48.

8. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114:10–31.

9. Asgari Z, Rouholamin S, Nataj M, Sepidarkish M, Hosseini R, Razavi M. Dose ranging effects of pregabalin on pain in patients undergoing laparoscopic hysterectomy: A randomized, double blinded, placebo controlled, clinical trial. J Clin Anesth 2017;38:13–7.

10. Jiang HL, Huang S, Song J, Wang X, Cao ZS. Preoperative use of pregabalin for acute pain in spine surgery: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96:e6129.

11. Li F, Ma J, Kuang M, Jiang X, Wang Y, Lu B, *et al.* The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty: a meta-analysis. J Orthop Surg Res 2017;12:49.

12. Karube N, Ito S, Sako S, Hirokawa J, Yokoyama T. Sedative effects of oral pregabalin premedication on intravenous sedation using propofol target-controlled infusion. J Anesth 2017;31:586–92.

13. Chavush MA, Yağar S, Ertürk A, Özgök A. Preliminary investigation of preoperative pregabalin and total intravenous anesthesia doses: a randomized controlled trial. J Clin Anesth 2017;41:137–40.

14. Gupta P, Saxena A, Chaudhary L. Effect of pregabalin premedication on the requirement of anesthetic and analgesic drugs in laparoscopic cholecystectomy: randomized comparison of two doses. Anesth Essays Res 2017;11:330–3.

15. Hetta DF, Mohamed MA, Mohammad MF. Analgesic efficacy of pregabalin in acute postmastectomy pain: placebo controlled dose ranging study. J Clin Anesth 2016;34:303–9.

16. Fujita N, Tobe M, Tsukamoto N, Saito S, Obata H. A randomized placebo-controlled study of preoperative pregabalin for postoperative analgesia in patients with spinal surgery. J Clin Anesth 2016;31:149–53.

17. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth 2012;15:18–25.

18. Gupta K, Bansal P, Gupta PK, Singh YP. Pregabalin premedication - A new treatment option for hemodynamic stability during general anesthesia: A prospective study. Anesth Essays Res 2011;5:57–62.

19. Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: A dose response study. Indian J Anaesth 2012;56:49–54.

20. Memiş D, Turan A, Karamanlioğlu B, Seker S, Türe M. Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol 2006;23:686–90.

21. Kohli M, Murali T, Gupta R, Khan P, Bogra J. Optimization of subarachanoid block by oral pregabalin for hysterectomy. J Anaesthesiol Clin Pharmacol 2011;27:101–5.

22. Steinberg AC, Schimpf MO, White AB, Mathews C, Ellington DR, Jeppson P, *et al.* Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. Am J Obstet Gynecol 2017;217:303–313.e6.

23. Kim JC, Byun S, Kim S, Lee SY, Lee JH, Ahn S. Effect of preoperative pregabalin as an adjunct to a multimodal analgesic regimen in video-assisted thoracoscopic surgery: A randomized controlled trial. Medicine (Baltimore) 2017;96:e8644.

24. Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. Can J Anaesth 2016;63:283–9.

25. Yücel A, Ozturk E, Aydoğan MS, Durmuş M, Colak C, Ersoy MO. Effects of 2 different doses of pregabalin on morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind clinical trial. Curr Ther Res Clin Exp 2011;72:173–83.

26. Rajappa GC, Vig S, Bevanaguddaiah Y, Anadaswamy TC. Efficacy of pregabalin as premedication for postoperative analgesia in vaginal hysterectomy. Anesth Pain Med 2016;6:e34591.

27. Raj PG, Amingad B. Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy. Indian J Clin Anaesth. 2016;3:374–9.

28. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, *et al.* Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 2010;50:941–50.

29. Wang YM, Xia M, Shan N, Yuan P, Wang DL, Shao JH, *et al.* Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy: A meta-analysis. Medicine (Baltimore) 2017;96:e7714.

30. Grant MC, Betz M, Hulse M, Zorrilla-Vaca A, Hobson D, Wick E, *et al.* The effect of preoperative pregabalin on postoperative nausea and vomiting: a meta-analysis. Anesth Analg 2016;123:1100–7.

31. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003;105:133–41.

32. Yosry M, Shafi ME, Othman AR. Premedication with oral pregabalin 150 mg reduces propofol sedation during retrobulbar anesthesia for vitrectomy surgery. Eur J Anaesth. 2008;25:132–3.

33. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009;108:1140–5.

34. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009;108:1140–5.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Nesrine A. El-Refai and Jehan H. Shehata designed the study, acquired and analyzed data and prepared the manuscript; Ahmed Lotfy performed the statistical data, figures and tables; Ahmed M. Elbadawy, Tamer M. Gamaleldin, Reham A. Abdel Rahman, Nasser M. Dobal, Tahani A. Farrag, Yaser M. Shafik and Adham F. Kamal helped to conduct the study, acquired data and drafted the manuscript; Ahmed A. Mohamed: analyzed data and prepared the manuscript.

Acknowledgments.—We thank the preoperative and operating room staff at Obstetrics and Gynecology, Cairo University Hospital for their assistance with the study.

Article first published online: September 13, 2019. - Manuscript accepted: September 4, 2019. - Manuscript revised: July 5, 2019. - Manuscript received: March 19, 2019.