Patients and methods

This randomized controlled study was conducted in kasr -Alainy Hospi tal, Faculty of Medicine. Cairo University. After obtaining approval form the Ethics and Research Committee, an informed written consent was taken from 50 female patients, aged 18 -60 years, ASA physical status I or II, scheduled for elective abdominal hysterectomy surgery under general anesthesia.

Patients younger than 18 or above 60 years old, patients with (ASA) physical status $\geq$ III, patients with compromised cardiovascular, renal, hepatic or neurological function and who were allergic to pregabalin were exclude d. In addition, patients recei ving calcium channel blockers, anti-convulsant, oral hypoglycemic agents or any analgesic or sedatives were excluded from the study.

Patients were randomly allocated to two study groups, 25 per group, using a random computer allocation with numbered closed opaque envelopes.

Pregabalin group (Gp): patients received oral pregabal in capsule single dose 150 mg 1h pre-operatively.

Control group (Gc): Patients received oral placebo capsule single dose 1h pre -operative.

The night before surgery through history -taking a nd clinical examination were done.Laboratory tests were ordered and reviewed pre-operatively:

- Complete blood picture.
- Liver function tests.
- Kidney function tests.
- Bleeding profile.

Solid food was not allowed 6 hours before surgery, but clear fluids were given for up to 4 hours pre-operatively.

The day of surgery patients attended at the pre-anesthesia room 2 hours before the procedure. Standard monitoring (electrocardiography, pulse oximetry and non-invasive blood pressure monitoring) were applied to the patients and basal hemodynamic measurements (oxygen saturation, systolic, diastolic and mean BP and HR were measured and recorded. A 20 Gauge cannula was inserted peripherally and all patients received intravenous Ranitidine 50 mg and Metoclopramide 10 mg.

Patients were pre-medicated orally 1h before surgery with the study medication pregabalin capsule 150 mg (G_P) or identical empty capsule as placebo (G_C) given with sips of water.

Randomization was done using a computer-generated random numbers. The study drugs, were further packed and sealed in opaque plastic containers labeled with randomized number, each consenting patient received a consecutive randomization number.

The anesthesiologist administering drugs and conducting anesthesia was blinded to the drug administered.

Bi-Spectral Index monitor (COVIDIEN BIS Monitoring system P/N 185-0151) was applied by using commercially available disposable Bis-Sensor strips (Aspect Medical Systems). The strips used four electrodes, three active and one ground. Placement on the forehead as follows: sensor 1 in center of forehead, approximately 2 inches (5cm) above the bridge of the nose, the 3rd sensor directly above the eyebrow, the 2nd sensor between 1st and 3rd, and the 4th on temple between corner of eye and hairline. The algorithm within the BIS monitor had

limits for electrode impedance and signal quality, and no BIS value was displayed if the signal has too much noise or artifact. The anesthetic depth, with an objective level of 40 –60 during the maintenance p hase and a level of 60 –70 during the last 10 minutes of surgery, was maintained.

The anesthetic protocol was standardized for all patients. Anesthesia was induced with, fentanyl (1 mcg/kg), thiopental sodium (5 -7 mg/kg IV) (till the abolition of the eyelash reflex) and Atracurium (0.5 mg/kg). Laryngoscopy and intubation were done a fter 3 minutes when the patient was at a sufficiently deep level of anesthesia (BIS < 60) and hemodynamic parameters recorded.

After endotracheal intubation, a nesthesia was mai ntained using Isoflurane in a mixture of oxygen and air and Atracurium (0.1mg/kg) every 15 minutes for muscular relaxation. Intra -operative IPPV ventilation is used MAQUET Flow-I anesthetic machine to maintain PaCO2 within normal range.

Isoflurane concentra tion was adjusted to maintain intra -operative hemodynamic stability (blood pressure and heart rate ± 20% of baseline), BIS value in the range 40 –60 during the operation and 60 –70 in the last 10 minutes of surgery. Hemodynamic parameters were measured and r ecorded immediately after intubation and after 3min, 5min, 10min and e very 15min till extubation. Hemodynamics parameter out of rang ±20% of baseline in the presence of normal end tidal CO2 were treated with additional doses of fentanyl (0.5mcg/kg). The response was checked after 10min non responders were managed by the incremental increase of Isoflurane till hemodynamic normalization. Intra -operative consumption of Isoflurane was measured and recorded (ml/ hr).

At the end of surgery, residualNeuro -muscular paralysis was reversed with neostigmine (0.04 -0.08mg/kg) and atropine (0.01 -0.02mg/kg) and surgical time was checked and recorded.

Post-operatively hemodynamics checked and recorded immedi ately after extubation, at 3min and 10min. Post-operative pain was a ssessed using the Visual Analogue Score (VAS) (0-10cm) (VAS; 0 = no pain and 10 = worst imaginable pain). Visual analogue score (VAS) ≥ 6 was controlled using pethidine 1mg/kg IM. (2)

The time to first rescue analgesia and total analgesic requirements were recorded. Post -operative side effects, including nausea and vomiting, headache, blurring vision, dizziness and sedation were checked and recorded in the recovery room 1, 2, 4 and 6 h post -operatively. Over sedation was define d as a score ≤ 2 on a 5-point scale (1):

Score 1 (barely arousable): Asleep, needs shaking or shouting to arise.

Score 2 (asleep): Eyes closed, arousable with soft voice or light touch.

Score 3 (sleepy): Eyes opened, less active, and responsive.

Score 4: Awake.

Score 5: Agitated.

Statistical analysis:

Sample size:

A Previous study showed that 1 h pre -operative oral pregabalin versus placebo reduced intra -operative i nhalational an esthesia by 0.9 versus 1.2 with standard deviation ± 0.31 (1). The sample size was calculated using Student's t -

test. Taking a power of the study of 80% and alpha error of 0.05, a minimum number of 20 patients will be needed for each group. T his number will be increased to 25patients per group to compensate for possible dropouts.

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student t test for independent samples. For comparing categorical data, Chi -square (C2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

1. Gupta P, Saxena A and Chaudhary L. Effect of pregabalin premedication on the requirement of anesthetic and a nalgesic drugs in laparoscopic cholecystectomy: Randomized comparison of two doses. Anesthesia. 2016 October2017; 11(2);330-333.

2. Mishriky BM, Waldron NH and Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta -analysis. British journal of anesthesia. 2015 Jan; 114(1); 10-31.