

**Use of oral pregabalina as preemptive analgesia in abdominal
hysterectomy: evaluation of postoperative pain in a
randomized clinical trial.**

Register Clinical Trials (clinicaltrials.gov): NCT04495374

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METHODS

Study design

This study is revealed to be an experimental, randomized, double-blind, controlled placebo controlled clinical trial. The trial included only female patients, who would undergo abdominal hysterectomy surgery under spinal anesthesia, where after randomization as patients they were allocated into two groups, the placebo controlled group (P0) and the pregabalin 300 mg group (P1).

The entire study had been carried out a research protocol in accordance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT). The revised CONSORT statement in 2010, consists of a list of 25 items in a table that configure a checklist with guidelines for the development of randomized clinical trials with parallel groups, this statement also contains a flowchart to guide the experimental design of the study.

Study location and period

All procedures, procedures and data collections for this study were carried out at Santa Casa de Alfenas - MG (Casa de Caridade Nossa Senhora do Perpétuo Socorro). The inclusion of patients in the study and the collection of data from September 2019 to September 2020.

Sample population

Initially the sample size was out of base from a pilot study carried out with 10 patients, where establishing a 95% confidence level and a power above 80% using non-parametric tests (Mann-Whitney test) for primary study outcomes, to decide to make an initial allocation of 51 patients in each study group, totaling 102 patients. These 10 patients in the pilot study were also included in the final version of the study.

Prepared to an atypical health scenario issued by the pandemic of COVID-19, during the year of 2020, in the month of September of that same year to choose to carry out new statistical analyzes with a population included so far in the study. From these new analyzes, the results obtained were statistic for the primary outcomes and due to difficulties imposed by the pandemic caused by the coronavirus, it was decided to interrupt the data collection at this time, totaling a total of 55 patients included in the study.

The inclusion criteria are detailed below, where all are mandatory, and also the criteria and exclusion used to define the sample population.

Inclusion criteria: (1) Female patients; (2) Age between 20 and 65 years; (3) Patients who will undergo elective abdominal hysterectomy surgery due to benign pathologies; (4) Be classified as physical status by the Society of Anesthesiologists (ASA) as ASA I (healthy individual) or ASA II (patient with mild and controlled systemic disease);

Exclusion criteria: (1) Allergy or known intolerance to pregabalin or opioids; (2) Patients with chronic pain or fibromyalgia; (3) Patients on chronic use of opioids; (4) carriers of malignant neoplasms; (5) Pregnant women; (6) People with active uncontrolled cardiovascular disease; (7) Patients with kidney and / or liver disease; (8) Patients who have spinal deformities that make spinal anesthesia impossible; (9) Presence of coagulation disorders or anticoagulant therapy that cannot be suspended for surgery; (10) Presence of active sepsis;

After accepting to participate in the study and signing the informed consent form, the sociodemographic data of all patients were collected through a questionnaire, for further analysis.

Groups and interventions

As this is a randomized clinical trial, this study was made up of two groups. The group P0, the group designated as placebo controlled, and the group P1, consisted of patients participating in the intervention group.

Group P0: Received two placebo tablets composed of starch and aerosil (colloidal silicon dioxide).

Group P1: They received two tablets identical to the tablets in group P0, but in this case, the tablets were each composed of pregabalin in the 150mg dosage, totaling a total dosage of 300mg of pregabalin.

All tablets were made in the same pharmacy handling, under conditions provided for in good manufacturing practices, to avoid bias.

Blinding

In order to avoid measurement bias, after elaboration, the tablets were placed in opaque and sealed envelopes, being identified only as formula A or formula B. An external researcher, who was not involved in randomization or data collection, was responsible by blinding, being the only researcher to know the composition of each formula. At the end of the study, this researcher informed the rest of the team of the composition of each formula, with Formula A consisting of two tablets of 150 mg of pregabalin each, and Formula B consisting of two placebo tablets.

Since the patients included in the study, the researcher responsible for medication randomization and administration, and also the researcher responsible for monitoring and collecting data, did not have knowledge about the composition of the interventions (formula A and formula B).

Randomization

After determining the sample population and preparing interventions in sealed and opaque envelopes, the randomization procedure had been carried out. To carry out the random allocation process, an external researcher was responsible for administering to the patient a sealed, opaque envelope containing the intervention (placebo or pregabalin 300mg) over a period of 02 hours prior to the start of the anesthetic-surgical procedure, with randomization it was simple, carried out by entering the study, where the first patient to be admitted to the study received formula A intervention, and the second received formula B, and so on. Another researcher was responsible for the patient's perioperative follow-up and data collection.

Experimental draw

A total of 58 patients were selected for the research. After randomization, 30 patients were allocated to the P0 group (placebo), but during the follow-up two were excluded, one due to the use of subarachnoid morphine and the other due to the use of analgesic medications (tramadol) in the immediate postoperative period, which was not included in the study protocol. In the P1 group (pregabalin 300mg), 28 patients were allocated, in which one patient had to be excluded due to the use of subarachnoid morphine during anesthesia. Thus, the analyzes were performed with a total of 28 patients in the P0 group and a total of 27 patients in the P1 group.

Evaluation procedures and measures

After the patient inclusion process, blinding and random allocation to groups were carried out. The patients participating in the P0 group received a sealed envelope containing two placebo tablets, while patients belonging to the P1 group received an identical envelope containing two tablets of 150mg pregabalin each, all tablets were administered within two hours prior to the start of surgery. , in the nursing room where the patients were hospitalized.

In the operating room, venoclysis was performed with jelco No. 18 or No. 20, and an infusion of 08 ml.kg-1 of crystalloid solution (lactated ringer). The patients were properly monitored with pulse oximetry, cardioscope, and non-invasive blood pressure monitor. After monitoring, patients were premedicated with intravenous (IV) midazolam at a dosage of 0.03 mg.kg-1

To perform spinal anesthesia, the patients were seated on the surgical stretcher by the nursing team. Asepsis and antisepsis were performed at the puncture site with alcoholic chlorhexidine solution. After placement of sterile drapes, local anesthesia was performed with 2.0% lidocaine without vasoconstrictor. The first attempt at subarachnoid puncture was performed, using the median technique, between the intervertebral levels L3-L4 or L4-L5 or L5-S1, with a 25G Quincke needle for subarachnoid anesthesia. In case of technical difficulty in the puncture, the paramedian puncture technique was chosen. The confirmation of the correct puncture was based on the aspiration of cerebrospinal fluid. Anesthesia was performed with the local anesthetic 0.5% bupivacaine at a dosage of 0.3 mg.kg-1, injected from a 5 ml disposable syringe. After anesthesia, the patients were placed in the supine position, and the correct level of anesthesia was proven with thermal sensitivity tests using cotton soaked with alcoholic solution. After the anesthesia reached the sensory level of the T4 thoracic vertebra, the surgical team was allowed to start the procedure. Prior to the beginning of the surgical incision, a delayed bladder probe was performed in all patients according to the surgeon's indication. All surgeries were performed by the same team of surgeons.

Hemodynamic changes in blood pressure were controlled with the use of vasoactive medications such as ephedrine or metaraminol. For prophylaxis of postoperative nausea and vomiting (PONV) ondansetron was administered at a dosage of 4 mg intravenously (IV) 30 minutes before the end of surgery. It was prescribed for all

tenoxicam patients at a dosage of 20 mg IV at regular intervals every 12 hours for the purpose of anti-inflammatory and analgesic action. For analgesic relief, dipyrone IV was also prescribed at a dosage of 50 mg.kg⁻¹ at regular intervals every 6 hours. During the surgery, and also at the end of the surgery, the patients were evaluated for the degree of sedation using the Ramsay sedation scale as a basis.

At the end of the surgery, the patients were referred to the PACU, where they were monitored again, and went through the pain assessment process using the visual analog scale (VAS) in relation to pain at rest and “movement” (the patient was asked to perform the forced cough movement), through a direct question with scale demonstration. Pain characterized as mild (0 - 2 VAS) received no medication, in addition to those already prescribed; pain characterized as moderate (3 - 7 EVA) received IV morphine at a dosage of 0.025 mg.kg⁻¹; and severe pain (8 - 10 VAS) received IV morphine at a dosage of 0.05 mg.kg⁻¹ every 01 h until analgesic control. To be considered able to be discharged from the PACU for clinical follow-up in wards, patients should reach a score ≥ 9 on the modified Aldrete Scale (Table 3) and have VAS pain scores ≤ 2 .

Upon arriving at the infirmary, patients were periodically evaluated at regular intervals in relation to the intensity of pain, with the help of a team of properly trained and qualified nurses. For patients who presented moderate-intensity pain (VAS $\geq 2 < 8$) or pain classified as severe (VAS ≥ 8), IV morphine was administered at a dose of 1 mg and 2 mg, respectively, according to a medical prescription. All analgesic medications used were recorded in the patient's medical record. 24 h after discharge from the PACU, in the ward, the patient was evaluated by the same examiner who performed the evaluation in the PACU, who again performed the stratification of pain by VAS and an evaluation with the McGill questionnaire.

During the entire hospitalization period of the study patients, the use of CNS depressant drugs (example: ketamine, droperidol, promethazine) and / or analgesic drugs that are not included in the study protocol was avoided. If any of the patients were medicated with such drugs, they would be excluded from the study to avoid bias in the statistical analysis. The data related to surgery (pre, trans and postoperative) were collected for statistical analysis, according to Annex II, in which, for example, the total duration of surgery in minutes was described; the total of intravenous fluids infused; the values of mean arterial pressure and heart rate in the pre, intra and postoperative period;

the presence or not, as well as the quantity, of PONV in the PACU and after 24h; presence or not of dizziness as a possible side effect, among others.

Outcomes

The primary outcome was the assessment of postoperative pain using two different scales, the traditional visual analog scale (VAS) and the McGill Pain Questionnaire. The secondary outcome was the comparative analysis between the groups of opioid consumption in the postoperative period, evaluating both the total dosage of opioids used, as well as the time between the end of surgery and the request for the first analgesic rescue dose.

Other outcomes that were analyzed, apart from the variation in patients' hemodynamic data during the surgical times (pre, intra and immediate postoperative period), the degree of sedation was also evaluated using the Ramsay scale, and the presence of side effects such as nausea and vomiting, itching and dizziness. Other independent variables were analyzed, such as age, weight, body mass index, education level, profession, family income.

Ethical aspects and records

This study with the objective of preserving the patients' physical and psychological integrity followed the statements enunciated by the Declaration of Helsinki. All patients previously admitted to the study were clarified about the methodological process, the randomization and blinding process, the guarantee of confidentiality, about possible side effects of the interventions and also about the risks and benefits of participating in the study and the consent costs for participation in it. After clarifying any doubts and consenting to the patients' participation, the free and informed consent form (ICF) was signed, to which one of the copies was delivered to the patient and another copy was filed with the study researchers.

According to Resolution No. 466 of December 12, 2012, of the National Health Council, which addresses the guidelines and regulatory standards for research involving human beings, this study was approved by the Research Ethics Committee (CEP) of UNIFAL- MG under opinion number 3,334,050 on June 17, 2019 (ANNEX IV). This research was also recorded in the North American database for the registration of clinical trials, Clinical Trials (clinicaltrials.gov), under the protocol NCT04495374.

Statistical analysis

Descriptive analysis (median, mean and standard deviation) was performed for continuous variables that followed a standard distribution, and these were expressed in a table.

When analyzing parametric variables, the t test was used, and in comparisons between groups, the t test was used for independent samples, and in the analysis of data at different points in time between patients in the same group, we chose to use the test. t paired.

When evaluating non-parametric variables, the Mann-Whitney test was chosen. To compare numerical measurements between the times in each group, the Wilcoxon test was used for the related samples. To assess qualitative variables, Pearson's chi-square test or Fisher's exact test was chosen.

All data obtained were digitized and analyzed using the Statistic® 7.0 software, with a significance level of 5% ($p < 0.05$). For the elaboration of statistical graphs, the program used was the GraphPad Prism version 5.00 (Trial) of 2007.