TITLE: PHASE IV CLINICAL TRIAL, RANDOMIZED AND CONTROLLED ON THE ANALGESIC EFFICACY OF THE COMBINED BLOCK (PENG -PERICAPSULAR NERVE GROUP- AND OF THE FEMORAL LATERAL CUTANEOUS NERVE) IN HIP FRACTURES OF THE ELDERLY. COMPARATIVE STUDY BETWEEN LEVOBUPIVACAINE AND ROPIVACAINE.

Protocol Code: **PENG-CAD**

EudraCT Number: **2020-004697-21**

Version Number**: 1**

Release Date: **September 1, 2020**

Development phase: **IV, low level of intervention**

Promoter: **IBSAL**

Principal Investigator***:*** **Agustín Díaz Álvarez**

PROTOCOL SIGNATURES PAGE

PENG-CAD Protocol

I have read this protocol and agree to supervise and direct the conduct of this study in compliance with all the stipulations of the protocol and in accordance with the Directives on Good Clinical Practice of the International Conference on Harmonization (ICH) and the Declaration of Helsinki.

Ms. María Lorenzo Santiago (Representative of the Promoter of the study)

_____ _____

Signature Date

Mr. Agustín Díaz Álvarez (Principal Investigator)

_____ _____ _____

Signature Date

MAIN INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: PHASE IV, RANDOMIZED AND CONTROLLED CLINICAL TRIAL ON THE ANALGESIC EFFICACY OF THE COMBINED BLOCKADE (PENG -PERICAPSULAR NERVE GROUP- AND THE FEMORAL LATERAL CUTANEOUS NERVE) IN HIP FRACTURES OF THE ELDERLY. COMPARATIVE STUDY BETWEEN LEVOBUPIVACAINE AND ROPIVACAINE.

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EudraCT Number: 2020-004697-21

CONFIDENTIALITY AND DECLARATION OF CONFORMITY OF THE PCBS

I have read the protocol of the previous clinical study entitled: PHASE IV, RANDOMIZED AND CONTROLLED CLINICAL TRIAL ON THE ANALGESIC EFFICACY OF THE COMBINED BLOCKADE (PENG -PERICAPSULAR NERVE GROUP- AND THE FEMORAL LATERAL CUTANEOUS NERVE) IN HIP FRACTURES OF THE ELDERLY. COMPARATIVE STUDY BETWEEN LEVOBUPIVACAINE AND ROPIVACAINE and I agree that it contains all the necessary information to carry out the study.

I hereby confirm that I have thoroughly read and understood this clinical study protocol, and I agree that my staff and I will conduct the study in accordance with the protocol and comply with its requirements, including ethical and safety considerations.

I understand that if the Promoter decides to terminate or suspend the study prematurely for any reason, such decision will be communicated to me in writing. On the other hand, if I decide to withdraw from the implementation of the study, I will immediately communicate that decision to the Sponsor.

I agree not to publish any portion of the results of the study conducted under this clinical study protocol without the prior written consent of the Sponsor.

Principal Investigator: Agustín Díaz Álvarez

Hospital Center: University Healthcare Complex of Salamanca

Signature

Date

Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)
University Hospital of Salamanca
Virgen de la Vega Building, 10th floor Pº San Vicente, 55-182.
37007 Salamanca

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ABBREVIATIONS

AAG: Serious Adverse Event

AEMPS: Spanish Agency for Medicines and Health Products

NSAIDs: Non-Steroidal Anti-Inflammatory

AL: Local Anesthetic

ASA: American Society of Anesthesiologist

BPC: Good Clinical Practice

BCFI: Iliac Fascia Compartment Block BNF: Femoral

Nerve Block

BNFCL: Femoro Nerve BlockLateral Body CAUSE:

University Care Complex of Salamanca CCAA:

Autonomous Communities

CEIC: Clinical Research Ethics Committee

CEIM: Ethics Committee of Research with Medicines CRD:

Data Collection Notebook

CTCAE: Common Terminology Criteria for Adverse Events

ECG: ElectroCardioGram

EVN: Numerical Visual Scale

IBSAL: Biomedical Research Institute of Salamanca ICCA:

ItelliSpace Critical Care and Anesthesia

ICH: International Conference on Harmonisation

IECSCYL: Instituto de Estudios de Ciencias de la Salud de Castilla y León

IQR: InterQuartil Range

NFCL: Cutaneous Femoral Nerve Lateral

NVPO: Postoperative Nausea and Vomiting

PAINAD: Paint Assessment in Advanced Dementia

PENG: PEricapsular Nerve Group

SatpO2: Peripheral Oxygen Saturation

SEDAR: Spanish Society of Anesthesiology, Resuscitation and Pain Therapeutics TA:

Blood Pressure

URPA: Post-Anesthetic Reuperation Unit

1. SUMMARY AND GENERAL INFORMATION

1.1. TYPE OF APPLICATION

Non-commercial Phase IV clinical trial of low level of intervention.

1.2. IDENTIFICATION OF THE SPONSOR

Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL).

IECSCYL-IBSAL Foundation.

1.3. TITLE OF THE CLINICAL TRIAL

Phase IV clinical trial randomized and controlled on the analgesic efficacy of the combined block (PENG - pericapsular nerve group- and the femoral lateral cutaneous nerve) in hip fractures of the elderly. Comparative study between Levobupivacaine and Ropivacaine.

1.4. PROTOCOL CODE

PENG-CAD.

1.5. MAIN INVESTIGATOR

Agustín Díaz Álvarez. Anesthesiology and Resuscitation Service. CAUSE. Biomedical Research Institute of Salamanca (IBSAL).

1.6. CENTRES WHERE THE STUDY IS PLANNED

University Care Complex of Salamanca.

1.7. CEIM

Ethics Committee of Research with Medicines Health Area of Salamanca.

1.8. RESPONSIBLE FOR MONITORING

The sponsor shall designate the monitor to monitor the progress of the test

Coordinator in the Promoter: Carmen Arias De La Fuente. Clinical Trials Area. IBSAL.

1.9. DESCRIPTION OF THE STUDY PRODUCTS

Group R (Ropivacaine), Group L

(Levobupivacaine) Route of administration:

perineural ecoguided.

1.10. CLINICAL TRIAL PHASE

Phase IV of low level of intervention.

10.11. OBJECTIVES

Main: To compare the analgesic efficacy of both local anesthetics in the regional blockade of hip fracture surgery in the elderly.

Secondary: 1) Describe the behavior of this combined technique in hip fractures, establishing latency of onset and duration of analgesia.

2) Describe the side effects derived from the described combined technique.

1.12. STUDY DESIGN

Prospective clinical trial (phase IV) of low level of non-commercial intervention, comparative of balanced, randomized groups, to compare the analgesic efficacy of the local anesthetics Ropivacaine and Levobupivacaine in peripheral nerve block in hip fracture surgery of the elderly.

1.13. STUDY DISEASE

The hip fracture of the elderly, subjected to both partial prostheses and endomedullary nailing.

1.14. STUDY VARIABLES

A. Main endpoint: duration of nerve block (analgesic efficacy of the two local anesthetics).

B. Secondary variables:

1. analgesia latency
2. duration of analgesia
3. adverse effects of the drugs used
4. scores of the analgesic scales: EVN, Algoplus, PAINAD.

1.15. STUDY POPULATION AND TOTAL NUMBER OF PATIENTS

Patients over or equal to 65 years of age who are going to undergo hip surgery for fracture.

The necessary sample size will be 108 patients, 54 patients per branch (Ropivacaine and Levobupivacaine), assuming 10% of losses.

1.16. DURATION OF PROCESSING

The duration of the treatment of each patient will be considered until the evaluation of the analgesic scale corresponding to the 48 h of the performance of the procedure. Patients may also be discontinued from the study at the discretion of the investigator at an earlier time or if they withdraw their consent at any time.

1.17. CLINICAL TRIAL SCHEDULE

From October 2020 until full recruitment. Approximately 15 patients/month will be recruited, which would mean a total of 7 months, that is, until April 2021.

1.18. COLLABORATING INVESTIGATORS OF THE TRIAL

Mr. Alberto de Diego Fernández. Anesthesiology and Resuscitation Service. CAUSE.

Mr. Daniel Escobar Macías. Anesthesiology and Resuscitation Service. CAUSE.

Dr. D. José Luis González Rodríguez. Anesthesiology and Resuscitation Service. CAUSE.

Ms. Rocío López Iglesias. Anesthesiology and Resuscitation Service. CAUSE.

Mr. Daniel Salgado García. Anesthesiology and Resuscitation Service. CAUSE.

Mr. Eduardo Sánchez López. Anesthesiology and Resuscitation Service. CAUSE.

Mr. David Sánchez Poveda. Anesthesiology and Resuscitation Service. CAUSE.

Mr. Ignacio Trejo González. Anesthesiology and Resuscitation Service. CAUSE.

2. INTRODUCTION

The increase in life expectancy together with very low birth rates is causing an accelerated growth in the percentage of older people, which results in an increase in the aging of the population, especially in the industrialized world. In our country, the phenomenon of aging is even more accelerated, since in less than 30 years the number of people over 65 years of age has doubled. Current data in Spain show that the population over 65 years of age is around 17% of the total population, with more than 7 million people (National Institute of Statistics-INE, 2008), of which approximately 25% are octogenarians. As a consequence, it is increasingly common to find in clinical practice elderly patients who require treatment of diseases and complications that are typical of advanced age.

Among these is the hip fracture, which presents a serious problem of morbidity and mortality for patients, and has a great impact on health costs due to both its treatment and the complications derived. It is estimated that there are 1.6 million fractures per year worldwide, with more than 610,000 fractures per year in Europe, and in Spain 45,000 fractures occur annually in older people(1, 2) of 65 years, being 80% over 75 years of age and with an associated annual mortality of about 30%(3, 4). Hip fracture is one of the most frequent surgical diagnoses in our environment. A very old and multipathological population, generally polymedicated and in which the presence of neurodegenerative diseases is not uncommon, makes it a very fragile population, which can sometimes have difficulty expressing its feelings, including pain, which is usually underdiagnosed(5). We must offer these patients an effective analgesic treatment from the first moment, avoiding the use of opioids and any drug that may deteriorate their cognitive faculties, and minimizing the use of usual analgesics (some of them, such as NSAIDs, can affect the control of blood pressure and already decreased renal function). Pain control in these patients is very important because it facilitates post-surgery recovery and early mobilization, and reduces the time of hospitalization after surgery, and the appearance of complications such as delirium, infections or thromboembolism(6). In addition, it accelerates the initiation of rehabilitation and functional recovery of elderly patients.

The debate on the most appropriate anesthetic technique for the surgery of the hip fracture of the elderly is still valid, between general and neuraxial anesthesia(7-11), as well as the different peripheral blocks combined or not with general or neuraxial anesthesia(12-16). Different anesthetic techniques have been used, such as femoral nerve block -BNF-, iliac fascia compartment block -BCFI-, lateral cutaneous femoral nerve block -NFCL-, among others. Although all of them have been shown to be effective in the surgery of the hip fracture of the elderly, they are insufficient in analgesic control.

Pain is a problem of special relevance in the elderly patient. It is estimated that between 50-80% of those over 65 years of age suffer some type of pain(17). Due to the presence of pluripathology and functional impairment, they become patients of great fragility who may also have cognitive impairment associated with them. In this type of patients the assessment of pain becomes complicated, being of enormous importance to be able to make a correct approach to the patient and achieve an adequate analgesic control. To all this, it is added that all scales and questionnaires have limitations, being convenient the assessment of more than one for the correct evaluation of the painful process(18-21). Thus, we will use 3 assessment scales: Visual Numerical Scale (EVN), Algoplus Scale (ALGSC), and Paint Assessment in Advanced Dementia Scale (PAINAD).

Since 2018, it has become popular to perform a technique known as PENG (pericapsular nerve group) that, because it affects only sensory endings, should not cause any degree of motor block of the affected nerves(22-25). This last aspect is of special interest, since muscle weakness due to femoral nerve block has traditionally been responsible for patients' falls when they begin postoperative ambulation.

Despite evidence that peripheral nerve blocks, and PENG in this case, are beneficial to the patient, neither adequate doses nor local anesthetic (AL) have been determined(13, 23, 24, 26, 27).

2. JUSTIFICATION OF THE STUDY

2.1. RELEVANCE OF THE STUDY

The realization of the PENG technique for the surgical management of the hip fracture of the elderly, has been incorporated into the usual practice, because it offers an adequate analgesia for the mobilization of the patient, makes it necessary to have a lower dose of local anesthetic in the spinal block, and achieves a correct postoperative analgesia, allowing the early mobilization of the patient without pain. Although performing surgery requires the help of other anesthetic techniques, peng blockade allows us to use fewer doses of anesthetics intrathecally, which translates into better hemodynamic stability, both intra and postoperative. Likewise, the postoperative analgesia that it produces will avoid the consumption of concomitant analgesia, avoiding pharmacological interference, with less risk of toxicity, both hepatic and renal.

We have at our disposal different local anesthetics that can be used in the nerve block, and, although with a series of common characteristics, they differ in some pharmacological aspects, which can be translated into the cynical one in that the selection of a certain local anesthetic can have an impact on the time of initiation of surgery, in which better or worse analgesic control is achieved, and in which the duration of said analgesic is greater or lesser duration and intensity in the postoperative period.

However, there is no scientific evidence of which local anesthetic is appropriate, nor what would be the ideal doses that would produce the balance between good analgesic control and minimal side effects.

In addition, it is intended to validate the assessment of pain in the elderly by combining three scales: EVN, Algoplus, PAINAD.

2.2 STUDY DRUGS

2.2.1 ROPIVACAINE

Ropivacaine is a long-acting local amide-type anesthetic with both analgesic and anesthetic effects, approved in our country since March 2012. At high doses it produces surgical anesthesia, while at low doses it causes a sensory block accompanied by a limited and non-progressive motor block.

The mechanism is a reversible reduction of the permeability of the nerve fiber membrane to sodium ions. As a consequence, the rate of depolarization decreases and the threshold necessary to produce excitation is increased, resulting in a local blockage of nerve impulses.

The most characteristic property of ropivacaine is the prolonged duration of action. The onset and duration of action of local anesthetic efficacy depends on the site of administration and dose, but are not influenced by the presence of a vasoconstrictor agent (e.g. adrenaline (epinephrine)).

Ropivacaine is indicated in the treatment of acute pain in adults and adolescents over 12 years of age in: Continuous epidural perfusion or intermittent bolus administration during the postoperative period or in labor pain; Peripheral locks; and Continuous peripheral nerve block by continuous infusion or intermittent bolus injections, e.g. treatment of post-surgical pain.

For the treatment of postoperative pain, ropivacaine can be used for epidural block using an epidural catheter, so that adequate analgesia can be achieved with only a slight and non-progressive motor block in most cases of postoperative pain with a moderate to severe character. The maximum duration of the epidural block is 3 days, and a significant reduction in the need to use opioids has been observed. It can also be used in association with fentanyl for the treatment of postoperative pain for a period of up to 72 hours. The combination of Ropivacaine and fentanyl may provide better pain relief, but cause side effects of opioids.

Ropivacaine is well tolerated and does not require adjustment in patients with impaired renal function when administered for single-dose or short-term treatment. It is metabolised in the liver and should therefore be used with caution in patients with severe liver disease. Cytochrome P450 (CYP) 1A2 is involved in its metabolism, so potent CYP1A2 inhibitors, such as fluvoxamine and enoxacin, may interact with Ropivacaine and concomitant use should be avoided.

The adverse reaction profile of Ropivacaine is similar to that of other long-acting local amide-type anaesthetics and varies by route of administration. The most frequently reported adverse reactions, nausea and hypotension, are very common during anesthesia and surgery in general and it is not possible to distinguish those produced by the clinical situation from those caused by the drug or blockage. In addition, common adverse reactions of paresthesias, dizziness, headache, bradycardia, tachycardia, hypertension, vomiting, stiffness, back pain, urine retention, temperature elevation, and chills have been reported.

2.2.2 LEVOBUPIVACAINE

Levobupivacaine is a long-acting local amide-type anesthetic with both analgesic and anesthetic effects, approved in our country since November 2013.

It works by blocking nerve conduction in sensory and motor nerves largely due to interaction with cell membrane voltage-gated sodium channels, but also blocks potassium and calcium channels. In addition, Levobupivacaine interferes with impulse transmission and conduction in other tissues where effects on the cardiovascular and central nervous systems are the most important for the occurrence of clinical adverse reactions. The dose of Levobupivacaine is considered equipotente with bupivacaine.

Levobupivacaine is indicated in adults in Major Surgical Anesthesia (e.g. epidural, intrathecal, peripheral nerve block) and Minor (e.g. local infiltration, peribulbar block in ophthalmic surgery) and for the treatment of pain (in continuous epidural perfusion, single or multiple bolus epidural administration for the treatment of pain, especially post-surgical pain). In analgesia (e.g. epidural administration for the treatment of pain) the lowest concentrations and doses are recommended. When deep or prolonged anaesthesia with complete motor block (e.g. epidural or peribulbar block) is required, the highest concentrations may be used. Careful aspiration is recommended before and during injection to avoid intravascular injection.

The maximum dose should be determined by assessing the size and physical condition of the patient, along with the concentration of the drug and the area and route of administration. There is an individual variation in the onset and duration of the block. Experience gained in clinical trials shows that sensory block suitable for surgery occurs within 10-15 minutes after epidural administration, with a regression time in the range of 6-9 hours. In the treatment of post-surgical pain, the dose administered during surgery should be taken into account. When used for regional major nerve block, the lowest effective dose of local anesthetic should be used to avoid high plasma levels and serious adverse reactions.

There are no relevant data on Levobupivacaine in patients with hepatic impairment, although it is metabolised in the liver, and should be used with caution in patients with liver disease or reduced hepatic blood flow. Levobupivacaine is extensively metabolized without detecting unchanged Levobupivacaine in urine or feces.

There are no data in patients with renal impairment. It should be used with caution in debilitated patients, elderly patients or acute patients, and also in patients receiving antiarrhythmic drugs with local anaesthetic activity (e.g. mexiletine, or class III antiarrhythmic drugs) because its toxic effects may be additive.

Experience on the safety of treatment with Levobupivacaine for more than 24 hours is limited. The adverse reaction profile of Levobupivacaine is similar to that of other local amide-type anesthetics. Adverse reactions with local amide-type anesthetics are rare, but may occur as a result of overdose or unintentional intravascular injection and may be serious. Some adverse reactions reported are very common during anaesthesia and surgery in general and it is not possible to distinguish those caused by the clinical situation from those caused by the drug or blockage. The most commonly reported adverse reactions are nausea and vomiting, hypotension, dizziness, headache, fever, pain during the procedure, or back pain. Cases of prolonged weakness or sensory disorders, some of which have been permanent, have been reported associated with treatment with Levobupivacaine. It is difficult to determine whether the long-term effects were the result of drug toxicity or unnoticed trauma during surgery or other mechanical factors, such as catheter insertion and manipulation.

2.3. JUSTIFICATION OF THE SELECTED VARIABLES

There are several studies that try to identify the ideal anesthetic for the management and control of pain from hip fracture surgery in the elderly. The optimal thing would be to use an anesthetic with the lowest possible latency, since this will favor the start of surgery. And, at the same time, with a more lasting analgesia with the least motor involvement. Therefore, it is essential to collect efficacy data (effective blockade that allows us to mobilize the patient), latency and analgesic scales appropriate to the cognitive state of the study sample.

3. HYPOTHESES AND OBJECTIVES

3.1. HYPOTHESIS:

Levobupivacaine has advantages over Ropivacaine in the combined blockade (PENG - pericapsular nerve group- and the femoral lateral cutaneous nerve -BNFCL-) in hip fractures of the elderly, since a better analgesic control, similar latency period, and a longer analgesic duration are obtained.

3.2. OBJECTIVES:

3.2.1. MAIN:

- To compare the analgesic efficacy of both local anaesthetics in the regional blockade of hip fracture surgery.

3.2.2. SECONDARY:

- To describe the behavior of this combined technique in hip fractures, establishing latency of onset and duration of analgesia.
- Describe the side effects derived from the described combined technique. To
- validate in our population, especially in patients with cognitive impairment, the usefulness of the analgesic scales chosen.

4. TYPE OF STUDY

A phase IV study of low level of intervention, open, prospective, randomized and controlled is proposed that aims to compare the analgesic efficacy of the proposed locoregional anesthetic techniques (PENG AND BNFCL) with two of the most frequently used local anesthetics in patients with hip fracture (Levobupivacaine and Ropivacaine) to whom surgical osteosynthesis (endomedullary interlocking or hip hemiarthroplasty) will be performed. The study begins in the preoperative period, applying an anesthetic protocol in the operating room and then followed up for at least 48 hours in the postoperative period.

The necessary sample size will be 108 patients, 54 patients per branch (Ropivacaine and Levobupivacaine). This figure could be increased to X patients in case of 10% losses due to complications during surgery.

5. JUSTIFICATION OF LOW LEVEL OF INTERVENTION

The medicines (Levobupivacaine and Ropivacaine) studied in this project are used in accordance with the authorised SmPC.

In the present trial, no additional procedures are performed with respect to those that would have been performed on participants in the context of routine clinical practice, both in Spain and in the European Union and other international settings.

6. MATERIAL AND METHODS

6.1. SCOPE OF STUDY

Unicentric study, which will be carried out in the Anesthesiology and Resuscitation Service of the CAUSA.

6.2. STUDY PERIOD AND RECRUITMENT PLAN

Start in October 2020 until the number of patients is completed. A rate of 15 patients/month is calculated, which means an expected completion in April 2021.

Patients will be selected from among the elderly with hip fracture who come to causa. Patients will be provided with detailed informed consent in plain language for review and given sufficient time to answer all questions related to the study. After signing the consent, it will be checked if they are eligible for the study according to the inclusion and exclusion criteria.

6.3. INCLUSION CRITERIA

- The patient will have to voluntarily sign and understand the informed consent that will be provided to him in writing.
- Patients over 65 years of age, with hip fracture, who are going to be operated on at the University Care Complex of Salamanca (CAUSA).

6.4. EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria will not be eligible to participate in this study:

- Rejection of the technique.
- Allergy to any of the drugs. Coagulation
- disorders. Local infections instead of
- puncture. Vascular prostheses at the
- femoral level.

6.5. RANDOMIZATION PROCESS

Randomization will be performed by means of a computer program (SPSS© v. 25.0) that generates two treatment groups and randomly assigns the selected patients to each of the groups in a simple random way (1:1).

6.6 . WITHDRAWAL CRITERIA FOR STUDY SUBJECTS

Patients will be removed from the trial when they meet any of the following criteria:

- Withdrawal of consent
- Complications during surgery that in the opinion of the researcher invalidate the results of the study
- Lack of collaboration or inability to evaluate the pain scales used in the study.

Patients who leave the trial for any reason may not be re-included. At the time of leaving the trial, the main reason for withdrawal of the trial must be recorded. The data collected up to the time of withdrawal may be included for analysis of results.

6.7. MEASUREMENTS

- Demographic variables: age, sex, weight, height, comorbidity (ASA grade).
- Variables related to the injury: subcapital fracture, pertrochanteric, subpertrochanteric or others.
- Variables related to the type of surgery: partial hip arthroplasty, endomedullary nailing or others. Duration of surgery.
- Variables related to the response:
    - Latency: evaluated by analgesic scales up to 10 minutes.
    - Analgesic scales: EVN, Algoplus and PAINAD at rest and in activity. They will be carried out upon the patient's arrival at the operating room, continuous until 10 minutes after the nerve block, in the sedation for the subarachnoid block, when they are discharged from the URPA, and at 6, 12, 24 h after the realization of the block, and end of effect after the realization of the block.
    - Need and rescue drugs: rescue analgesia will be scheduled for the hospitalization floor, in case it is necessary. The need, drug and time of administration regarding the realization of the blockade will be collected (Annex II).

6.8. ANESTHETIC PROTOCOL

- After giving informed consent to the patient or his guardian, the patient is monitored according to the usual standard (SEDAR Protocol, which includes ECG, TA, SatpO2).
- The ultrasound-guided block at the femoral level (PENG) is performed in the patient's transfer bed or table, depositing 20 cc of local anesthetic, with a 50-80 mm needle (depending on the anatomical characteristics) and a low-frequency probe. Next, a 50 mm needle and the high-frequency ultrasound probe will be used to block the NFCL by depositing 5 cc

of the same anesthetic, always without exceeding the maximum recommended dose for each drug. (See Annex I).

- Latency in the establishment of analgesia in the affected territory is explored, as well as an assessment of pain (Numerical Visual Scale and Algoplus).
- We proceed to the realization of the intradural spinal anesthesia, assessing again the pain that manifests. Subarachnoid blockade will always be performed with the same dose: 5 mg of Bupivacaine 0.5% hyperbaric with 10 µg of Fentanyl.
- After the surgical intervention, he will be transferred to the URPA (Post-Anesthetic Recovery Unit) and, subsequently, to the hospitalization floor when his situation allows it. At all times the constants, the analgesic variables and the treatments that you have needed will be recorded. (See Annex II).

6.9. JUSTIFICATION OF SAMPLE SIZE

Taking into account the Pharmacokinetics of both local anesthetics, and previous studies(28, 29), using the G*Power program, the sample size is calculated. We consider significant a difference in the duration of the blockade of at least 3 h, with a deviation of 50%. The security level or alpha error is 5%. The beta error is 20%. A total of 108 patients were obtained, 54 in each of the lines of intervention, assuming 10% of losses.

6.10. STATISTICAL ANALYSIS

A descriptive analysis of the variables collected will be carried out. Non-categorical ones shall be expressed as median +/- IQR (interquartile amplitude). Categorical variables shall be expressed as percentages or frequencies.

After performing the relevant normality tests (Kolmogorov-Smirnov or Shapiro-Wilk), the sample differences will be determined by t-Student or Mann-Whitney U tests. In the comparison of pain scales we will use the analysis of variance (ANOVA or Kruskal-Wallis).

The comparative analysis of the categorical variables will be carried out by means of Chi-square tests with cross tables.

The control of the possible intermediate and confusing variables will be carried out by means of Multiple Linear Regression Analysis.

The significance level will be, by default, 5% ($p<0.05$).

All calculations will be carried out with the statistical program SPSS© 25.0 for Mac.

6.11. ASSESSMENT OF EFFICACY

The main endpoint of the study's effectiveness will be the difference in the duration of the blockade.

6.12. POLICY REGARDING INTERMEDIATE ANALYSES AND CRITERIA FOR EARLY COMPLETION OF THE TRIAL.

This clinical trial may be stopped earlier than expected by the result of an interim analysis demonstrating greater than expected benefit or harm in any of the treatment arms. 1 formal internal efficacy and safety analysis will be carried out when 50% of the expected number of participants are reached. Poor study performance (e.g., slow patient recruitment, high rates of follow-up losses, or poor quality control) may be another cause of early study discontinuation.

6.13. ASSESSMENT OF ADVERSE EFFECTS

6.13.1-DEFINITION OF ADVERSE EVENT:

An adverse event is defined as any event that occurs during the clinical study, whether it is either an intercurrent disease or accident, and that alters the well-being of the patient. The event may also take the form of a laboratory anomaly.

The term adverse event does not imply any causal relationship with the treatment of the study. All adverse events, including intercurrent diseases, will be reported and documented as described below.

Toxicities and adverse events shall be scored using version 5.0 of the CTCAE for reporting toxicity and adverse events.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

All participating researchers should have access to a copy of version 5.0 of the CTCAE.

6.13.2-CLASSIFICATION OF ADVERSE EVENTS:

Adverse events will be divided into the categories of serious and non-serious, which determine the procedure to be followed for the notification and documentation of the same.

a) Serious adverse events :

A serious adverse event is defined as anyone who threatens the life of the patient or causes death and also as one that causes disability, permanent disability or prolongs hospitalization. Any event involving congenital malformations or involving cancer is also serious.

b) Non-serious adverse events :

Adverse events that do not fall into any of the above categories will be classified as non-serious.

6.13.3-RELATIONSHIP WITH THE TREATMENT:

The investigator should try to explain each adverse event and assess its relationship with the trial treatment (probable, possible, unrelated). Criteria for establishing the relationship between clinical adverse reactions and study medication include:

3.1 *Likely*: If you meet the following three criteria:

1) There is a reasonable temporal relationship between the administration of the medicinal product and the adverse event.

2) The adverse event is a typical example of a known adverse drug reaction (If treatment is continued, the adverse event persists; if the drug is discontinued, the adverse event disappears; if a reexposure occurs, the adverse event reappears).

3) If there is another explanation of the adverse event (concomitant treatment, breakthrough disease), this explanation is less likely as the cause of the adverse event.

3.2 *Possible*: It is considered as an adverse reaction possibly related to the medication, one that meets the following two criteria:

1) There is a reasonable temporal relationship between drug administration and adverse event.

2) None of the criteria set out in point 2 above (probable) is met or there is another, more plausible explanation for the adverse event.

3.3 *Unrelated*: The adverse event will be classified as unrelated to the medication when it meets any of the following requirements:

1) There is no reasonable temporal relationship between the administration of the medicinal product and the onset of the adverse reaction.

2) The causal relationship between the medication and the adverse event is not biologically plausible.

3) There is another, more plausible alternative explanation for the adverse event.

4-Monitoring, reporting, and documentation of adverse events

-Non-serious adverse events

They will be recorded on the sheet dedicated for this purpose in the CRD of each patient, and no special notification procedure is necessary.

-Serious adverse events

All serious adverse events, regardless of their relationship to study treatment, should be reported as soon as possible, but no later than two working days. The *serious adverse event reporting form* should be sent to the study sponsor by email (*ensayosclinicos@ibsal.es*).

Deaths and life-threatening events should be reported immediately by telephone or email to the trial sponsor. Subsequently, the AAG notification form will be sent by email. Preliminary notifications of AAG should be followed as soon as possible by means of detailed descriptions, including copies of clinical reports, autopsy reports and other documents requested by the sponsor. In both cases a follow-up of the AGAs must be completed (until they are resolved) as soon as possible, and a new completed AAG form faxed to the sponsor It is very important that the AAG notification forms are as complete as possible from the time of the initial notification, including the investigator's assessment of causation. If the follow-up information changes the investigator's assessment of causality, it should be noted in the follow-up form. Any adverse events that the investigator believes are related to the treatment of the study should be reported to the sponsor, regardless of the time that has elapsed since the end of the study. It will be the obligation of the promoter to notify the AGAs in the terms and forms according to current legislation to the competent authorities, AEMPS, CC.AA and CEICs involved.

6.14. DATE AND SOURCE DOCUMENTS

6.14.1. MEDICAL HISTORY

The data will be collected from the electronic medical record (Jimena IV) and, where appropriate, the paper medical record. Also part of the medical record are the records of the ICCA applications.

6.14.2. WHAT IS CONSIDERED A SOURCE DOCUMENT IN THIS ESSAY

Source Data: All information in original documents and certified copies of original records of clinical results, observations, or other activities of a clinical trial necessary for the reconstruction and evaluation of the trial. The source data will be included in the source documents (original records or certified copies).

Source documents: original documents, data and records (e.g., patient records, medical or consultation records, laboratory notes, memoranda, records, data recorded on automated instruments, certified copies or transcripts after verification, microfiche, photographic negatives, microfilm or magnetic media, radiographs, subject files and pharmacy records in laboratories and in medical-technical departments involved in the clinical trial).

Patients must have allowed their medical history to be read in writing by staff authorized by the sponsor and regulatory authorities. This information is included in the informed consent.

6.14.3 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Promoter shall sign appropriate agreements to appoint a monitor who will supervise this study and shall periodically contact the centre, including the management of visits to the centre. The researcher agrees to allow the monitor direct access to all relevant documents and to devote his or her and his or her staff's time to the monitor to comment on the results and any matters of interest.

6.14.4 QUALITY CONTROL AND ASSURANCE

In order to ensure the quality of the data, the sponsor shall:

- Instructions and quality training will be provided to the research staff before the start of the study. Training topics include, but are not limited to: GCP certificates, AA reports, study details and procedures, study documentation, informed consent, and patient recruitment.
- Perform regular monitoring in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP). The data will be evaluated for adherence to protocol and accuracy relative to the source documents. The monitors will verify that the clinical trial is carried out, that the data is generated, documented and reported in compliance with the protocol, good clinical practice and any applicable local regulatory requirements.

Direct access to the data will be granted to the principal investigators, monitors, members of the evaluating CEIm and the AEMPS, as well as to the authorities that are necessary, in order to allow monitoring and surveillance related to the study, audits and inspections. At each center, they will be able to review the study records and compare them directly with the source documents, they could discuss how to conduct the study with the researcher, and verify that the facilities remain acceptable. Audit reports shall be treated confidentially

7. ETHICAL AND LEGAL ASPECTS AND OBTAINING INFORMED CONSENT

This study has been designed in accordance with the general ethical principles set out in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013). The researchers will carry out the study in accordance with the Good Clinical Practices (PCB), described in harmonized Tripartite Guidelines of the ICH of Good Clinical Practices and the Document of instructions of the Spanish Agency of Medicines and Health Products for the conduct of clinical trials in Spain (Version 9 of July 27, 2018).

The researcher will prepare the documents to request evaluation by the Ethics Committee of Research with medicines of the Health Area of Salamanca, and will respond, where appropriate, to the request for clarifications. Approval of the CEIm will be obtained before the start of the study. The study will be notified to the Spanish Agency for Medicines and Health Products (AEMPS).

The researcher will facilitate the performance of monitoring visits and audits by the Promoter, reviews of the CEIm, and regulatory inspection(s) if necessary, providing direct access to the facilities where the study was carried out, to the source documents, to the CRDs, and to all
other study documents.

The investigator shall obtain the informed consent of a patient or his/her legal representative before initiating any procedure related to the study, in accordance with the PCBs, as stipulated in the ICH guidelines. It will be recorded in the patient's source documents (medical history) that informed consent has been obtained prior to the patient's entry into the study. The original consent form, signed and dated by the patient and by the investigator will be kept in the study investigator's file. When the investigator proposes to the patient his inclusion in the study, he will inform him in depth about the objectives, possible risks and benefits of his participation, he will answer all the questions that the patient may ask, who will have time to decide his participation in the study. When the patient is legally incapacitated or is not in a position to sign the consent, his legal representative will do so, in accordance with the hospital's policy and the legislation in force in this matter. In the event that a family member signs the consent because the patient is not in a position to sign the consent, and is not legally incapacitated, consent will be requested as soon as possible, when he meets the appropriate conditions, to ratify the consent given by his family.

8. DATA PROTECTION AND CONFIDENTIALITY

REGULATION (EU) No 536/2014 requires that subject data be treated in accordance with Union data protection legislation. In Spain, Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights, complementary to Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of these data and repealing Directive 95/46/ CE. This legislation requires the application of high-level security measures in the handling of health data, so that the distribution of the media is carried out by encrypting said data or using another mechanism that guarantees that said information is not accessible or manipulated during its transport.

Study data will be protected and confidentiality will be maintained in accordance with current legislation. Patients will be identified by a code and only the research team, qualified personnel in charge of monitoring, health authorities, or other authorized third parties may review the medical records of patients. The code used will not allow the identification of the subject, and will not include or collect identifying data such as the medical record number or similar assigned by the Administration, the name, surname, initials of the subject, the postal address or email address, the telephone number, the tax identification number, the fingerprint, THE DNA, a photograph, the social security number, ...

The collected data (CRD) will be stored encoded in a database hosted on causa's servers, under the supervision of the principal investigator. Causa servers are subject to security controls and regulations in accordance with hospital policy and applicable data protection regulations.

The researcher will ensure that the records and documents of the study as original signed consents, any type of source document (hospital records, medical records, ultrasound records of *the procedure* datos de laboratorio...) y CRD, will be kept for the time required by current legislation. Likewise, you agree to comply with the procedures of conservation of documents / records by signing the protocol.

9. PROTOCOL CHANGES

If a modification to the test protocol is necessary, the modification or a new version of the trial protocol (modified protocol) will be notified to the CEIm of the Salamanca Health Area, to be approved by it before its application.

10. ANALYSIS AND COMMUNICATION OF RESULTS

The analysis of the data will be carried out by the research team and will be communicated in meetings and scientific articles in peer-reviewed journals. Regardless of the results of the study, the sponsor agrees to present them to the medical community through scientific publications, congresses or other means.

ANNEX I. - ANESTHETIC PROTOCOL

• Standard patient monitoring in the operating room.

• Intravenous sedoanalgesia for puncture. We will not use, and in any case we will avoid long-acting benzodiazepines (if essential Midazolam 0.5-1mg).

• Ultrasound puncture with patient in supine position, without moving him in bed.

• Anesthetics to use:

  • -Group R: Ropivacaine 0.375% (25 cc): will be administered: 20 cc for PENG and 5 cc for BNFCL

  • -Group L: Levobupivacaine 0.25% (25 cc): 20 cc will be administered for PENG and 5 cc for BNFCL.

• Assess latency: explore until pain disappears on passive mobilization. maximum 10 minutes.

• Performance of the subarachnoid block in a sitting position on the operating table. Dose: 0.5% hyperbaric bupivacaine (5 mg) + 10 µg of Fentanyl.

• Record the required surgical variables on the collection sheet.

ANNEX II.- RESCUE ANALGESIC TREATMENT:

- Review patient treatment in URPA and in the hospitalization floor. **Do not administer scheduled analgesia** unless the patient demands it, and for the same reason always leave **a scheduled rescue** . If necessary, notify the Resident of the Anesthesiology Guard (Virgen de la Vega Hospital building). Evaluate your pain and write down the elapsed time.
- **Paracetamol** 1 gr/ 6 h iv. If contraindication or allergy: Metamizol 2g/8 h iv.
- If you need more analgesia and the 6 h has not passed:
- **Dexketoprofen** 50 mg iv/ 8 h.
- If contraindication to NSAIDs or pain persists:
- **Ondansetron** bolus 4mg iv and **Tramadol** infusion 200 mg iv + **Metamizol** 6 gr diluted in 500 cc S. Physiological to pass in 24 h (20ml/h). And discontinue Paracetamol, except in those allergic to Metamizole.
- Follow-up of the patient 48 h.

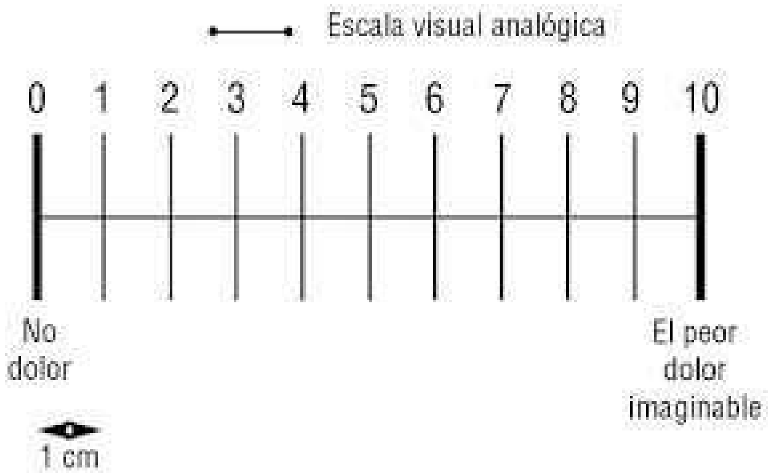

Figure 1. Numerical Visual Scale

They do not wish to have elements of illustrations.

ESCALA ALGOPLUS

Evaluación del comportamiento frente al dolor

Niveles o gradaciones de evaluación del comportamiento frente al dolor agudo en las personas mayores con problemas de comunicación verbal

Identificación del paciente

Fecha de evaluación del comportamiento frente al dolor	..../..../....		..../..../....		..../..../....		..../..../....		..../..../....		..../..../....	
Hora	....h		....h		....h		....h		....h		....h	
	SÍ	**NO**	**SÍ**	**NO**	**SÍ**	**NO**	**SÍ**	**NO**	**SÍ**	**NO**	**SÍ**	**NO**
1 • Rostro Fruncimiento del ceño, muecas, crispación, mandíbulas apretadas, parálisis facial												
2 • Mirada Mirada poco atenta, inexpresiva, perdida o suplicante, llanto, ojos cerrados												
3 • Quejas verbales « Ay », « Oh », « me duele », gritos y gemidos												
4 • Cuerpo Contracción corporal o protección de una parte del cuerpo, negativa a moverse o a desplazarse, actitudes estereotipadas												
5 • Comportamiento Comportamiento : agitación o agresividad, agarrotamiento												
Total SÍ	/5		/5		/5		/5		/5		/5	
Profesional de salud que ha realizado la evaluación	❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma		❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma		❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma		❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma		❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma		❑ Médico ❑ Enfermera ❑ Auxiliar de enfermería ❑ Otro Firma	

Figure 2. Algoplus Scale

PAINAD score

Items·	0		2	Score
Breathing independent of vocalization	Normal	Occasional labored breathing. Short period of hyperventilation.	Noisy labored breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low-level speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying.	
Fae to the exprtts on	Smiling or inexpressive	Sad. Frightened. Frown.	Facial grimacing.	
	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolab Ll Ty	No need to console	Distracted or reassured by voice or touch.	Unable to console, distract or reassure.	
			Tota"	

Figure 3. PAINAD scale

ANNEX III. DATA COLLECTION NOTEBOOK

Group	Levobupivacaine/Ropivacaine	
Hospital stay	In days	
Age	In years	
Sex	Female/Male	
Weight	In kg	
Size	In m	
Body Mass Index		
Type of Fracture	Subcapital/Pertrochanteric/Subpertrochanteric/Other	
Type of Surgery	Partial athroplasty/Interlocking/Other	
Duration of Surgery		
On arrival at the operating room	EVN/Algoplus/Painad	
Latency time		
When sitting	EVN/Algoplus/Painad	
At Discharge of Resuscitation	EVN/Algoplus/Painad	
At 6 o'clock from the blockade	EVN/Algoplus/Painad	
At 12 o'clock of the blockade	EVN/Algoplus/Painad	
Within 24 hours of the blockade	EVN/Algoplus/Painad	
At the end of the blockade	EVN/Algoplus/Painad	
Analgesic rescue	Drug used	
Minutes to rescue	Time elapsed from lock to rescue	
Morphic equivalence	Equivalence in morphics of the rescue used	
Nausea and vomiting		
Toxicity	Toxicity developed by local anesthetics	
Delirium		
Infection	Clinically and analytically diagnosed	
Exitus		

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