1 COVER PAGE

1.1 Official title:

Study Protocol (ID: NCT04385966) entitled “Diaphragmatic paralysis after interscalene brachial plexus block: a randomized, double-blinded, unicenter and controlled clinical trial to reduce the dose of levobupivacaine 0,25% 20 ml to 10 ml undergoing arthroscopic shoulder surgery”.

1.2 NCT number:

NCT04385966.

1.3 Document date:

February 10th, 2021.

CLINICAL TRIAL PROTOCOL

OFFICIAL TITLE

Diaphragmatic paralysis after interscalene brachial plexus block: a randomized, double-blinded, unicenter and controlled clinical trial to reduce the dose of levobupivacaine 0,25% 20 ml to 10 ml undergoing arthroscopic shoulder surgery.

1.4 NCT NUMBER

ClinicalTrials.gov register number: NCT04385966.

1.5 DOCUMENT DATE

ClinicalTrials.gov register date: 08 May 2020.

2 ADMINISTRATIVE INFORMATION

2.1 TITLE

Diaphragmatic paralysis after interscalene brachial plexus block: a randomized, double-blinded, unicenter and controlled clinical trial to reduce the dose of levobupivacaine 0,25% 20 ml to 10 ml undergoing arthroscopic shoulder surgery.

2.2 TRIAL REGISTRATION

EudraCT register number (register date): 2019-003855-12 (07 January 2020).

Spanish Trial Register (REec) (register date): 2019-003855-12 (07 January 2020).

Ethics Committee approval (approval date; responsible): EC19/093 (18 December 2019; Maria Gonzalez Hinjos [Ethics Committee Secretariat]).

Phase: III.

Protocol code: REDOLEV-2019.

Version (date): 1.0 (17 October 2019).

2.3 SPONSOR

Aragon Institute for Health Research (IISAragon). Address: Avenida San Juan Bosco 13, Edificio CIBA, Planta baja. Phone: +34 976 71 68 18 .

2.4 FUNDING

The institution where the study is enrolling is: Anestesia and Intensive care Departament. Hospital Universitario Miguel Servet (HUMS). Paseo Isabel la Católica, 1-3, 50009 Zaragoza, Spain. Phone: +34 976 76 55 00.

Aragon Health Sciences Institute (IACS) Instituto Aragonés de Ciencias de la Salud (IACS). Address: Calle de San Juan Bosco, 13, 50009 Zaragoza, Spain. Phone: +34 976 71 58 95. Email: dbordonaba.iacs@aragon.es.

In this clinical trial, the sponsor and the Principal Investigator (PI) state that no funding sources, no potential conflicts of interest, and no institutional affiliations of the researcher are available.

In accordance with the posterior defined methodology of this study and with the resources available in the HUMS, the development of the research project does not need any additional economic expenditure.

3 ABBREVIATIONS

- ADR Adverse Drug Reaction.
- AE Adverse Event
- AEMPS Spanish Agency of Medicines and Medical Devices
- ARP Assessment research physician
- CI Collaborator Investigator
- DCF Data Collection Forms.
- DMC Data Monitoring Committee
- DTR Diaphragmatic Thickness Ratio
- EDT Expiratory Diaphragmatic Thickness.
- GA General Anaesthesia
- HDPA HemiDiaphragmatic Paralysis Acute
- HUMS Hospital Universitario Miguel Servet
- IBPB Interscalene Brachial Plexus Block.
- IC Informed Consent.
- ICU Intensice Care Unit
- IDT Inspiratory Diaphragmatic Thickness.
- IRP IBPB research physicians
- LA Local anesthetic
- LBP Levobupivacaine
- NRS Numerical Rating Scale
- NSAID Non-steroidal anti-inflammatory drugs
- PACU Post-Anesthesia Care Unit
- PCA Patient-Controlled Analgesia
- PI Principal Investigator.
- PMR Participant Medical Record.
- RCT Randomized Controlled Trial
- RP Research Physician
- RRP Recruitment research physicians
- SADR Serious Adverse Drug Reaction.
- SAE Serious Adverse Event.
- SS Statistical staff
- ToF Train of Four
- UADR Unexpected Adverse Drug Reaction.

- US Ultrasound

4 INTRODUCTION

4.1 RESEARCH DRUG: NAME AND DESCRIPTION

Research Drug: Levobupivacaine (Chirocane®). FDA approval: NDA-20997 (1999).

Description: Levobupivacaine (LBP) is the S(-) enantiomer of the amide-type local anaesthetic Bupivacaine with a pharmacodynamic and an equivalent potency. However, LBP presents less neurological and cardiac toxicity with less prolongation of the QT segment and less negative inotropic effect Its onset of action is less than fifteen minutes and causes a sensory block of approximately 6 hours after intradural administration, 9 hours after epidural administration and 17 hours after peripheral nerve block with a dose of 2 mg/kg(1).

4.2 BACKGROUND AND RATIONALE

Shoulder surgery is a surgical procedure that involves dynamic pain, moderate or severe, in the postoperative period that can compromise the patient's early rehabilitation (2,3).

Brachial plexus blockade by interscalene approach (IBPB) is one of the most effective anaesthetic and analgesic techniques used in this type of surgery (4,5). According to the 10th International Classification of Diseases (ICD-10), it has the procedure code: 3E0T3CZ (3,6).

The main indications for IBPB are surgery of the shoulder joint, the two lateral thirds of the clavicle, the proximal part of the humerus, and as an anaesthetic complement in surgeries of the pectoral and dorsal areas of the thorax (2,3,7,8). In these cases, locoregional anaesthesia offers a better postoperative analgesic control, lower consumption of opioids, a lower economic cost, a lower incidence of nausea and vomiting and a shorter hospital stay (9).

On the other hand, the IBPB associates a series of complications such as phrenic nerve block, neuroaxial diffusion, total spinal block, vascular puncture, Bezold-Jarisch reflex, stellate ganglion block, recurrent nerve block, etc (7).

The absolute contraindications of IBPB are exceptional: patient rejection, allergy to local anaesthetics, local infection at the puncture site, or hemodynamic instability. However, relative contraindications are more common such as chronic obstructive pulmonary disease (COPD), contralateral phrenic nerve or recurrent paresis and a previous neurological deficit of the arm (2,8).

The diaphragm is the main inspiratory muscle when constrained it causes a caudal movement of the chest which results in inspiratory movement. It is responsible for the 75% increase in lung volume in normal breathing, compared to the remaining 25% that is the responsibility of the intercostal, scalene and sternocleidomastoid muscles. Its insertion at an inferolateral level of the thoracic cage is called the apposition zone. The ultrasound (US) visualization of the apposition zone in inspiration and expiration presents high rates of sensitivity and diagnostic specificity of hemidiaphragmatic paralysis acute (HDPA). The diaphragmatic paralysis can be categorized as: complete in case of a >75% decrease of the diaphragmatic excursion (DE) or a paradoxical DE, partial if there is a 25% to 75% decrease of the DE or null in case of a variation lower than 25% (10,11).

The diaphragm is innervated by the phrenic nerve, which originates from the C3-C5 nerve roots. This nerve can be blocked by the IBPB due to the rostral migration, volume dependent, of the local anaesthetic that will originate an ipsilateral diaphragmatic paralysis (4,9). Classically, Urmey et al. (1991) established that IBPB caused a 100% incidence of phrenic nerve block with subsequent ipsilateral diaphragmatic paralysis defined according to ICD-10 with code J98.6 (6,12). Nowadays, thanks to the advances in the techniques of nervous localization by US and the reduction of the dose of local anaesthetic required in these techniques of locoregional anaesthesia, the incidence of diaphragmatic paralysis has been reduced up to an interval of 13-47% according to recent publications. This literature provides very variable results so the contraindications of IBPB are still in force (4,13–16).

For the diagnostic evaluation of phrenic blockade, lung US is a non-invasive, reproducible, non-radiant and reliable tool (9,11). Recently, the measurement of diaphragmatic thickness has been published as a diagnostic tool for phrenic paralysis (15,17). By visualizing the apposition area with US, during inspiration and expiration, the inspiratory diaphragmatic thickness (IDT) and the expiratory diaphragmatic thickness (EDT) can be quantified. A normal EDT can range from 2.2-2.8 mm and a normal IDT can reach more than 4 mm. While IDT or EDT values below 2 mm indicate

PDA (17). Thus, from this US measurement, the IDT and EDT are obtained and then the ratio of inspiratory/ expiratory diaphragmatic thickness ratio (DTR) is calculated by the ratio of IDT/EDT. The DTR has a sensitivity of 93% and a specificity of 100% for the diagnosis of diaphragmatic dysfunction if it is lower than 1.2 (15,18).

Likewise, forced spirometry is a first-line diagnostic tool in the diagnosis of neuromuscular pathology such as diaphragmatic paralysis (19). Phrenic nerve block has been associated with a decrease of about 25% in respiratory parameters such as Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1), and 15% in the Peak Expiratory Flow (PEF) Rate (4,11). This side effect is usually well tolerated by most patients, but in those with a history of COPD, restrictive diseases, or obstructive sleep apnea-hypopnea syndrome or compromised breathing capacity may be a contraindication. Also, such respiratory compromise and the corresponding hypoxemia caused to have an impact on the patient's post-surgical comorbidity.

For this reason, this technique of locoregional anaesthesia is contraindicated in those patients with a history of severe respiratory pathology in whom this diaphragmatic paralysis cannot be assumed (8). Therefore, this type of patient is forced to undergo general anaesthesia, as the only possible anaesthetic option with the side effects that general anaesthesia and mechanical ventilation equally entails for this type of patient. However, locoregional anaesthesia offers numerous clinical and economic perioperative benefits over general anaesthesia (9).

To date, there are no published data in the literature about the respiratory impact of US-guided IBPB with local anaesthetic volume and objectified by respiratory and imaging functional diagnostic tests during the usual clinical practise of an anesthesiologist in Spain (15).

This study will try to objectify the diaphragmatic paralysis caused by the IBPB technique performed on patients undergoing scheduled arthroscopic shoulder surgery during the usual clinical practice of an Anesthesia Service in a third level hospital in our country. The aim is to describe the real respiratory and functional repercussion caused by this side effect of BPBHA at present, to assess the benefit-risk ratio and the relative contraindications of this anaesthetic technique in the future.

The evaluation of the benefit-risk of the intervention in this clinical trial (CD) is very satisfactory because there are two diagnostic tests available (diaphragmatic US and forced spirometry) that are non-invasive, bloodless, painless, and assistive that could

also be performed according to normal clinical practice. In the same way, the invasive technique that is carried out consists of the practice of the IBPB according to the usual clinical practice of the anesthesiologist so it does not involve more risk than usual. Therefore, there is no added risk for the patient-derived from the intervention proposed in this study.

However, the benefit that we seek to obtain is to know the incidence and the real clinical repercussion of the IBPB to evaluate in the future the contraindications of this locoregional technique used in our daily anaesthesia practice. Thus, patients with respiratory or nerve pathology who, to date, are forced to undergo general anaesthesia without locoregional support in shoulder surgery could be accepted and benefit from locoregional anaesthesia and analgesia in shoulder surgery, supported by evidence of the expected results.

In case we can objectify an incidence of diaphragmatic paralysis lower than the classic estimate of 100% as other scientific works are already recording, shortly, the contraindications of this anaesthetic technique could be reconsidered and the usual clinical practice of the anesthesiologist modified based on the evidence (15,20–22).

4.3 RISK-BENEFITS BRIEF

In this study, the intervention to be performed (IBPB with LBP) is an anaesthetic invasive technique carried out in the current practice at the Regional Anaesthesia Division of the Department of Anesthesia, Intensive care and Pain management in the Hospital Universitario Miguel Servet (HUMS).

This anaesthetic technique entails a series of risks and complications such as vascular puncture, peripheral nerve damage or systemic poisoning by local anaesthetics, risks that would also be assumed if the patient did not participate in this clinical trial, since the concentration, volume and dose of the intervention drug are the same as those used by normal clinical practice for carrying out this type of surgery.

The two diagnostic techniques used (US scan and spirometry) are assistive, non-invasive, painless and could be performed equally, even if the patient are not been enrolled.

This study does not include any invasive procedures added to the usual current practice for performing anaesthesia in patients scheduled for arthroscopic shoulder surgery.

4.4 ROUTE, DOSE AND TIME OF ADMINISTRATION: DESCRIPTION AND JUSTIFICATION

The medication for this study is Chirocane® 2.5 mg/ml Injectable and Infusion Solution. Its administration will be carried out following the technical datasheet of the Spanish Agency for Medicines and Healthcare Products (AEMPS) with the therapeutic indication in adults of surgical anaesthesia by peripheral nerve block (23).

In this study, the medication will be administered by an attending anesthesiologist specialized in the management of regional anaesthesia.

Chirocane® 2.5 mg/ml will be administered around the nerve while the attending anesthesiologist performs the peripheral nerve block needle (IBPB).

During the administration of the dose, the patient's vital functions will be monitored and measures will be taken to prevent blood puncture according to normal clinical practise (23).

10 ml and 20 ml of Chirocane® 0.25%, equivalent to a dose of 25 and 50 mg, respectively, will be administered. Thus, it will be administered according to its AEMPS datasheet. The 0.25% (2.5 mg/ml) concentration, the 10-20 ml volume and the 25-50 mg dose used are within the intervals allowed by the AEMPS datasheet. The amount of medicine allowed by AEMPS is a concentration of 2.5-5 mg/ml, a volume of 1-40 ml and a dose of 2.5-150 mg. Therefore, the maximum single dose of 150 mg allowed by AEMPS will never be exceeded (23).

The dosage pattern will be standardized by protocol, in a single dose, administered in bolus with a period of punctual treatment prior to surgery in the immediate preoperative where the surgical anesthesia of the peripheral nerve will be performed by means of a IBPB.

4.5 STUDY POPULATION: DESCRIPTION

The source of our population sample is all the patients undergoing an arthroscopic shoulder surgery at the Division of Shoulder Surgery attached to the Orthopaedics Department in the HUMS.

4.6 RESEARCH HYPOTHESES

- Ho: There is no statistically significant decrease in the incidence of acute diaphragmatic paralysis, quantified by the Diaphragmatic Thickness Ratio, after Interscalene Brachial Plexus Block with ultrasound-guided interscalenic approach in scheduled arthroscopic shoulder surgery after administration of a volume of 10 ml of Levobupivacaine 0.25% (dose 25 mg) compared to 20 ml of Levobupivacaine 0.25% (dose 50 mg).
- Ha: There is a statistically significant decrease in the incidence of acute diaphragmatic paralysis, quantified by the Diaphragmatic Thickness Ratio, after Interscalene Brachial Plexus Block with ultrasound-guided interscalenic approach in scheduled arthroscopic shoulder surgery after administration of a volume of 10 ml of Levobupivacaine 0.25% (dose 25 mg) compared to 20 ml of Levobupivacaine 0.25% (dose 50 mg).

5 OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary study objective is to determine the HDPA diagnosed by using diaphragmatic thickness index in US after Low Volume (10 mL) versus Standard Volume (20 mL) of Levobupivacaine 0,25% for IBPB.

5.2 SECUNDARY OBJECTIVES

Secondary end-points are: 1) HDPA diagnosed by using FVC and FEV1 in spirometry, 2) HDPA diagnosed by using diaphragmatic excursion in US, 3) postoperative pain regarding time to first analgesic consumption and 24-hour cumulative total consumption of Patient-controlled analgesia (PCA) pump of Morphine IV; (4) postoperative harms between two trial-arms; and (5) to perform a cost-analysis of the intervention of the study.

6 METHODS

The protocol of this clinical trial is conducted in concordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and the recommendations for Interventional Trials (SPIRIT) guidelines (24–26). This protocol is published elsewhere (27).

6.1 TRIAL SETTING

Patients will be recruited for the study only from Shoulder Surgery Unit and Orthopaedics Anaesthesia Division of the Hospital Universitario Miguel Servet (HUMS) in Zaragoza, Spain. HUMS provides health care to a population size of about 400000 inhabitants and about 80 arthroscopic shoulder surgery are performed every year. Enrollment began in 2020 and is anticipated to continue through 2021.

6.2 TRIAL DESIGN

The REDOLEV trial is designed as a randomized, comparative, prospective, phase III, unicenter, double-blind, two-arm and controlled Clinical trial (RCT). 48 patients scheduled for arthroscopic shoulder surgery under general anesthesia (GA) with interscalene brachial plexus block (IBPB) for postoperative analgesia will be included. Eligible patients will be randomly assigned to 2 groups: G1 (Control arm: Standard volumen dose will be 20 mL of 0,25% Levobupivacaine) or G2 (Treatment arm: Low volumen dose will be 10 mL of 0,25%Levobupivacaine).

6.2.1 VARIABLE TABLE

	TIMING			
	Pre IBPB	**Surgery**	**4-hour Post IBPB**	**24-hour Post IBPB**
PRIMARY VARIABLES	1. Inspiratory Diaphragmatic Thickness. 2. Expiratory Diaphragmatic Thickness. 3. Diaphragmantic Thickness Ratio.		1. Inspiratory Diaphragmatic Thickness. 2. Expiratory Diaphragmatic Thickness. 3. Diaphragmantic Thickness Ratio.	
SECONDARY VARIABLES	1. Informed consent date. 2. Randomization date. 3. Participant data. 4. Ultrasound data. **5.** Spirometry data.	1. Surgery data.	1. PACU data. 2. Ultrasound data. 3. Spirometry data. 4. Pain data.	1. Hospital data. 2. Spirometry data. 3. Pain data. 4. Safety data.

Tabla 1: Study Variables

6.3 ELEGIBILITY CRITERIA

6.3.1 INCLUSION CRITERIA

1. Patients aged 18 to 80 years.

2. ASA I-III.

3. Scheduled for shoulder arthroscopic shoulder surgery and interscalene brachial plexus block.

6.3.2 EXCLUSION CRITERIA

1. Age <18 and >80 years.
2. Pregnancy.
3. Exclusión to perform IBPB or spirometry.
4. Allergy to amide group local anaesthetics, opioids or nonsteroidal anti-inflammatory drugs.
5. Background of Pulmonary diseases (chronic obstructive pulmonary disease (COPD) and moderate, severe or not well-controlled asthma), diaphragmatic paralysis or neurological disease with diaphragmatic dysfunction, brachial plexus neuropathy or chronic opioid consumption (more than 3-months consumption or more than oral Morphine 1 mg 1-month).
6. Coagulation disorders (INR>3, TTPA > 35 y AP <50%).

6.3.3 WITHDRAWAL CRITERIA

Patients may be withdrawn from treatment and trial evaluations at any time. The specific reasons for a patient's withdrawal from this trial are :

1. Voluntary withdrawal at any time they wish, without this representing any type of harm to the subject in the subsequent treatments that may be required.
2. Safety reasons at the discretion of the investigator.
3. Significant non-compliance with the protocol, at the discretion of the investigator and coordinator.
4. Incorrect recruitment (the patient does not meet the inclusion/exclusion criteria) or incorrect randomization (the patient is not assigned trial medication according to the protocol).

Participants who withdraw their IC will be automatically withdrawn from the study, cannot be re-enrolled and the assigned patient number will not be reused. They will be asked the reason for their withdrawal, the presence of an adverse event (AE), and will be asked for their IC for their follow-up. These data will be recorded in the DCF.

Patients incorrectly included will be withdrawn from treatment if the BPBAI and other assessments (chest ultrasound and spirometry) have not been performed.

Post-treatment losses have been foreseen a priori in the statistical calculation of the sample size by means of an estimated 10% of the patient. Patients lost after being included and randomized in this CD will not be replaced and patient recruitment will continue until the sample size (n=48) established a priori is achieved.

The follow-up after the administration of the medication and the performance of the BPBAI lasts 24 hours post-operatively. It is performed in the hospital ward by means of clinical and spirometry evaluation.

6.4 INTERVENTIONS

Eligible patients will be randomised in equal proportions between low volumen dose (10 mL of 0,25% Levobupivacaine) group and standard volume dose (20 mL of 0,25% Levobupivacaine) group, receiving either only once as a single-shot IBPB in surgery theatre before arthroscopic shoulder surgery.

The two study-arm drugs will be provided and relabeled by Pharmacy Department of HUMS. After the trial recruitment, they will be checked and destroyed as current practice according to CEICA guidelines.

During the hospital stay, there will be four visits to the participants. Spirometry and US will be performed as baseline and post-intervention assessments. After surgery, Morphine IV PCA system will be administered to control postoperative analgesia. Every research physician in charge of US and spirometry assessments will be blinded to the IBPB intervention.

The interventions will be entirely integrated within routine clinical practice.

1. Interscalene Brachial Plexus Block (IBPB: MeSH Unique ID: D065527 and CIE-10 code 3E0T3CZ) will be performed with ultrasound-guidance using a variable frequency, linear transducer (GE Medical, Milwaukee, WI, USA). After sterile skin

preparation with chlorhexidine, an in-plane posterior approach with a 22-gauge 50 mm Stimuplex Ultra 360º needle will be used to deposit the study drug in the interscalene space, between the middle scalene and anterior scalene muscles and the brachial plexus, at the level of the sixth cervical vertebra. Before surgery commenced, IBPB success will be determined using sensory loss in the thumb and index fingers. Patients without evidence of brachial plexus block within 10 minutes of local anesthetic injection were excluded from analysis.

Hence the resulting 2 study groups will be as follows:

- Group Control: (Group 1) Standard Volume dose IBPB: 20 mL of 0,25% Levobupivacaine.
- Group Treatment: (Group 2) Low Volume dose IBPB: 10 mL of 0,25% Levobupivacaine.

2. Diaphragmatic US will be performed before (baseline) and 4-hour (1 hour minimum after extubation) after IBPB in a sitting and supinus position. Ipsilateral and contralateral hemidiaphragm of each patient will be imaged using a lineal ultrasound transducer (GE Medical, Milwaukee, WI, USA). Ultrasound apposition zone will be assessed in anterior axillary line and the diaphragmatic thickness will be recorded in maximal inspiration and espiratory. They will be expressed by Inspiratory Diaphragmatic Thickness (IDT) and Expiratory Diaphragmatic Thickness (EDT). ED will be evaluated on inspiration and expiration as number of intercostal spaces and motion type, expressed by normal/caudal, nule or cephalad/paradoxical motion of the diaphragm with inspiration.

3. Spirometry will be performed using a bedside spirometer (Air-Smart Spirometer; NuvoAir AB © 2020, Riddargatan 17D, SE-11457 Stockholm, Sweden) before (baseline) and 4 (1 hour minimum after extubation) and 24 hours after IBPB in sitting and supinus position. It will be performed in accordance with the standards of lung function testing of the American Thoracic Society (ATS) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) (28–30). Forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), FEV1/FVC ratio and peak expiratory flow (PEF) will be measured three times every assessment to obtain acceptable and reproducible criteria. Best FVC and FEV1 effort will be recorded.

Assessments will occur in 3 times, no depending on whether participants are assigned to the intervention group, as follows:

1. Assessment 1: After consent and randomization, baseline US and spirometry will be performed in hospital room.
2. Assessment 2: 4 hours post IBPB and 1 hour minimum post extubation US and spirometry will be performed in PACU.
3. Assessment 3: 24 hours post IBPB. Spirometry will be perform in hospital room.

4. Combined Locorregional-General Anaesthesia (GA): Before induction, the IBPB will be developed in surgery theatre. 2 g cefazoline will be given IV. All patients will receive an intravenously GA with Fentanyl 2 ug/kg, Propofol 2 mg/kg and Rocuronium 0,6 mg/kg. Patient will be orotracheally intubated and mechanical ventilation will be applied. Respiratory rate and tidal volume will be adjusted to keep the patient normocapnic. Bispectral index (BIS) and Train of Four (ToF) will be monitored. Anaesthesia will be maintained with Sevoflurane (0.7-1 MAC) to get a 40-60 BIS monitor. Intraoperative analgesia with Remifentanil IV (0.05–0.2 μg/kg/min) will be administered at the discretion of the attending anesthesiologist. Every patient will receive Paracetamol 1 g and Enantyum 50 mg IV. Dexametasone 8 mg and Ondansetron 4 mg IV as anti-emetic prophylaxis will be given. The fluid management with balanced crystalloids is aiming for normovolemia. Before extubation, if ToF 4/4 <90% Sugammadex 2 mg/kg will be used. After leaving surgery theatre, the patient will attend to PACU.

5. Arthroscopic shoulder surgery will be routinely performed arthroscopically by the same two surgeons with the patient in the beach chair position. No concurrent open repairs will be included.

6. Postoperative Patient-controlled analgesia pump (CADD®-Solis Infusion System, Smiths Medical, Minneapolis; USA) of Morphine IV will be administered in PACU. PCA will be delivered a 1 mg bolus (2 mL) with 10 minutes time-close without basal IV administration for 24-hour postoperative follow-up. Patient numeric rating scale (NRS) pain score (0-10) will be recorded after entry and discharge PACU and at 24 hours.

7. PACU Interventions: Room air oxygen saturation, US and spirometry will be assessed using the procedure described above. Patients will be discharged from the PACU after achieving an Aldrete score greater than 8 (of 10 possible points).

8. Hospital Interventions: During hospitalization, all the patients will receive 1 g Paracetamol and 50 mg Enantyum IV alternatively every 4 hours. 2 g Metamizol IV will be given in Participants with NSAID drugs allergic background. 4 mg Ondansetron IV

every 12 hours will be given as nausea and vomiting prophylaxis. After post IBPB, 24 hours Spirometry and an EVA score will be recorded for each patient. The follow-up will finish in postoperative 30 days with incidence, frequency and severity of Serious Adverse Events (SAE) and hospital admission reviews.

LA or other trial drugs allergic reactions could be observed in rare cases. If this is suspected withdraw the trial medication from the patient. This should be reported as an adverse event.

As active comparator, 24 patients will be enrolled in the Standard Volume Dose arm. 20 ml Levobupivacaine Hydrochloride 2.5 MG/ML will be administered in the IBPB before the arthroscopic shoulder surgery. As Experimental study arm, 24 patients will be included in the Low Volume Dose group. 10 ml Levobupivacaine Hydrochloride 2.5 MG/ML will be administered in the IBPB before the arthroscopic shoulder surgery.

6.5 OUTCOMES

The primary outcome of REDOLEV trial is 1) difference in the proportion of patients with HDPA according to DTR in US between the treatment and control groups. DTR will be the result of Inspiratory Diaphragmatic Thickness and Expiratory Diaphragmatic Thickness. The ratio will be defined by DTR=IDT/EDT. HDPA after IBPB at 4 hours will be diagnosed with a DTR<1.2 (15,18,31). The time frame will be between the baseline data and 4-hour after interscalene brachial plexus block.

Secondary study outcomes are the difference between the intervention and control groups: (1) in the proportion of patients with HDPA diagnosed in spirometry by using a diminution of ≥20% of baseline, 4-hour and 24-hour postoperative FCV and (2) FEV1, (3) in the proportion of patients with HDPA according to DE in US expressed by number of intercostal spaces (reduction ≥25%) and motion type (positive to paradoxal or nule diaphragmatic motion), (4) in postoperative 24-hour cumulative IV morphine consumption (mg) and (5) in time to first analgesic consumption (min) of Patient controlled analgesia (PCA) pump and (6) in the incidence, frequency and severity of (Serious) Adverse Events as assessed by CTCAE v4.0 (15,32–34). Every secondary outcome will be compared in each study group.

The time frame will be between the baseline data and 4-hour and 24-hour after IBPB.

For the cost-analysis, secondary outcomes will be the use of services and sick leave will be evaluated using the economic variables described above for the 12 months before and 1 month and 12 months after the study intervention. The cost of anesthetic management medications will be obtained from the hospital pharmacy department. Service use (medications, medical and laboratory tests, admissions, etc.) and sick leave of the patients evaluated will be obtained telematically from the hospital database. The average monetary costs (in €) of each of the interventions will be calculated after multiplying the use of health services or sick leave by the unit cost. The unit cost for the use of health resources and productivity losses will be confined to the context of the study intervention, i.e. the Aragonese Health System (SALUD) and the National Health System. The unit costs of the use of services will be extracted from the tariffs published in the Official Bulletin of Aragon of the Government of Aragon (35) and will be expressed in euros (€). Since not all tariffs are published in the same year, they will be updated using the sanitary retail price indexto the year 2021. To estimate the unit cost of sick leave, the average wage in Aragon and the minimum wage in Spain in 2020 will be used. Productivity losses will be calculated from the perspective of human capital (36,37). For the cost analysis, the health system perspective and the limited company perspective (health system perspective and sick leave) will be taken into account. A sensitivity analysis will be performed by varying the unit cost of sick leave.

This is a per Intention-To-Treat study.

6.6 SAMPLE SIZE

The sample size was calculated according to HDPA incidence after IBPB. Previous studies determined HDPA incidence after IBPB was always 100%(12,32). However, locorregional blocks have been improved for years thanks to US development. Recent studies have already referred that using low volume and concentration doses of LA in IBPB decreases the HDPA incidence (4,20,38,39).

This trial assumed a HDPA after IBPB rate of 90% in the control group, and 33% in the treatment group according to previous studies with similar LA Volumen and doses for IBPB (4,20,38). These findings suggest that after decreasing the IBPB LA dose hence (10 ml, 0,25% or 25 mg) we expect to find less HDPA after IBPB.

Therefore, in order to power this trial to detect a mean difference in HDPA after IBPB between two study groups of 90%-33%, with a two-sided significance level of 1% and

power of 90% with equal allocation to two arms would require 21 patients in each arm of the trial. To allow for 10% drop out, 24 will be recruited per arm, ie, 48 participants will be the total sample size using Epidat® software (40,41).

6.7 RECRUITMENT

Prospective participants of surgery waiting list will be screened through reviewing of health records by research physicians to determine eligibility in one study site. They will be recruited after hospital admission hours before surgery. Inclusion and exclusion criteria will be assessed for purposes of adhering to the Consolidated Standards of Reporting Trials (CONSORT) standards. Informed consent will be provided and the baseline evaluation that includes Common Assessment Battery, baseline spirometry and baseline US will be completed. Individuals who decline to participate will be asked to provide a reason as well as basic demographic information to facilitate comparison between study participants and those who are eligible but decline to participate.

An average of three adult patients consults per week for arthroscopic shoulder surgery. Through the REDOLEV trial, we will expect to successfully recruit and interview 48 patients in 12 months.

6.8 ASSIGMENT OF INTERVENTIONS

In this trial, four independent research physician teams will be part of: IBPB research physicians (IRP), Assessment research physician (ARP), Recruitment research physicians (RRP) and Statistical staff (SS).

All patients who give consent for participation and meet all the inclusion criteria and none of the exclusion criteria will be consecutively included by RRP. Participants will be randomly allocated with equal probabilities to both two study arms (control or treatment group) by IRP. IBPB performance and the administration of study drug will be carried out only by IRP. IRP will be a group of three anesthesiologists experienced in locorregional blocks. Spirometry and US assessments will be conducted by ARP, only one blinded anesthesiologist. This will decrease inter-operator variability.

The allocation sequence as per a random number table will have been generated using Epidat® software by SS. SS will conduct the study analyses.

6.9 RANDOMIZATION

An a priori randomized treatment assignment will be made using the Epidat computer software. The computer algorithm requires the number of treatments (2 treatments), types of groups to be created (groups of equal size) and a number of participants (48 cases) (40,42). The randomization table will be defined by the Epidat software before the start of Clinical trial recruitment.

During this study, two figures are involved: the PI and the Collaborator Investigators (CI). The PI will be responsible for recruiting the patient and verifying that the inclusion and exclusion criteria are met. A single CI will have access to the treatment randomization list and will be the only non-blind person in the CI. This non-blind CI will have the functions of verifying the treatment group corresponding to each participant recruited and preparing the medication attributed to each patient that will later be administered.

The PI and the other blind CIs will not have access to the treatment randomization list or the patient's medical history until after 24 hours post-operative. By that time, all US and spirometry measurements will have been made. At this point, the patient's perioperative data will be collected and the assigned randomization group will be unmasked.

The maintenance of the randomization codes will be achieved thanks to the independence of the non-blind CI from the IP and the rest of the CIs, operators of the measurements.

In case it is necessary to open the blind before performing the last follow-up measurement, the unblinded CI will reveal the treatment group assigned to the corresponding patient and the process, as well as its causes will be documented and explained in the Patient Medical Record (PMR).

One of the conditions under which the treatment codes may be opened is the appearance of a Serious and Unexpected Adverse Reaction (SAR), in which it is required to know the dose of medication administered for the clinical management of the patient. Some examples of pathologies that would require opening the randomization codes are systemic intoxication by local anaesthetics or serious respiratory complications.

Cases will be recruited according to their chronological order of surgical intervention according to which they will be randomly assigned to one of the two treatment groups according to the protocol (40,42).

6.9.1 BLINDING

A double-blind masking will be performed where neither the PI nor the operator performing the ultrasound and spirometry measurements will know the intervention group assigned to the patient until the end of the follow-up period 24 hours after all the measurements have been collected.

The highest quality ultrasound machine available in the hospital and a portable spirometer with European quality and validation certificates will be available.

6.10 DATA

The source data of this trial are the data from the perioperative US and spirometry measurements performed on each participant. The source data will be contained in the original files or certified copies of the source documents kept in the Departament of Anaesthesia in the HUMS.

The Data Collection Form (DCF), the test reports and PMR shall be considered source documents.

All measurements will be collected in the DCF by RRP and ARP.

As the primary outcome, HDPA will be observed by using DTR in US which provides a 93% Sensibility, 100% Specificity (15,17,18,31,43). US images will be interpreted in real-time and assessment data will be entered into the DCF. Every participant will be evaluated baseline and after-IBPB his block diaphragm and non-block side to have their own control in every assessment. Spirometry will be evaluated by using a certificated portable spirometer with a 79% Sensibility and 90% Specificity (15,32,33,44–48). It will be performed in supine and sitting position to increase the sensitivity and specificity (48). Postoperative pain will be measured and collected by using PCA pump record. PCA is decrease analgesic consumption, increases the patient satisfaction score and duration of effective analgesia (49–51). The incidence, frequency and severity of AE/SAE as assessed by CTCAE v4.0 will be recorded (34).

Every research personnel will be trained in the study requirements. ARP anesthesiologist has been training in diaphragmatic US for six months in advance.

Participants may withdraw from the study for any reason at any time. The PI also may withdraw participants from the study in order to protect their safety or if they are unwilling or unable to comply with required study procedures. Withdrawal reason will be asked, measured and figure in the DCF.

All write measurements will be duplicated in the DCF and in the Participant Medical Record (PMR). Spirometer and PCA assessments will have an additional electronic record in Spirometer phone app and PCA system. All data will be entered electronically to the database at the participating site. Statistical analysis will manage range checks for data values.

All study data will be hosted securely on the HUMS network, protected by several firewalls. A complete back up of the database will be performed monthly. Participant study files will be kept on file in storage for 25 years at the participating site.

6.11 STATISTICAL METHODS

Excell (Redmont, USA), IBM SPSS v.22 (Chicago, USA) and Open Epi v3.0.1 (Santiago, Spain) will be used to collect data and conduct analyses. For all analyses, a statistically significant result is assumed if $p<0.02$. We will use the Bonferroni method to appropriately adjust the overall level of significance for multiple primary outcomes, and secondary outcomes.

A descriptive analysis of the data will be performed: the qualitative variables (Sex, Surgical side, BPBAI complications, etc.) will be presented using the frequency distribution of the percentages of each category and the quantitative variables studied (Ultrasound and spirometer variables, etc.) will be explored with the Kolmogorov - Smirnov compliance test (Goodness-of-fit test to a normal distribution). Central tendency (mean or median) and dispersion (standard deviation or percentiles) indicators will also be given.

To respond to the main hypotheses raised in this study, the degree of association between the variables involved will be examined using graphical (scatter diagram) and analytical (simple correlation coefficient) methods. The interpretation of the intensity of

the relationship was carried out following the criteria established by Gerstman (2015) and Martínez-González et al (52,53).

Concerning bivariate analysis or comparison between two variables (factors), the association between the factors will be investigated using hypothesis contrasting tests. In the case that both variables compared were qualitative, a comparison of proportions with chi-square or Fisher's exact test will be used. In the case that one of them is quantitative, a comparison of means will be made using the Student t-test, ANOVA, and if they do not follow normal distribution the Mann-Whitney U-test or the Krustal-Wallis test. Likewise, a bivariate correlation (Pearson's Correlation) will be carried out when both variables are quantitative or, if the conditions of application are not fulfilled, a Spearman's correlation.

In some of the catalogued variables, where the case also serves as a control (before-after relationship): comparisons of means will be made for related samples when one of them is quantitative (t of Student, ANOVA for repeated measurements), and if they do not follow a normal distribution the Wilcoxon test or the Friedman test.

As for multivariate analysis, to study the relationship of each variable controlling for the possible effect caused by third variables, the analysis will be completed using regression models.

As an interim analysis will be performed, confidence intervals and hypothesis tests will be calculated according to the O'Brien-Fleming method.

The study drug will be provided by the Pharmacy Service of the HUMS as current practice.

6.11.1 Statistical analysis for the cost-analysis

The difference in healthcare use and costs between groups was assessed 1 month and 1 year after the intervention.

Due to the variable distribution and the high proportion of zeros in the sample, mean differences in healthcare use and days on sick leave between groups were estimated using two-part models. A preliminary logistic regression was applied to obtain the probability of using a given healthcare service. These analyses were followed by

generalised linear models with Poisson distribution performed conditional on the positive outcome of the first part. The models were controlled for baseline healthcare resource use (those incurred in the 12 months preceding the intervention).

The cost analysis was performed using generalised linear models (GLM) with gamma distribution with a logistic link and costs as the dependent variable. The models were controlled for baseline costs (those incurred in the 12 months preceding the intervention). Differences in time in the operating room and PACU between intervention and control groups were assessed through a t-test. Sample size estimation is in detail elsewhere.(54) For all analyses, a statistically significant result was assumed if $p<0.05$. Analyses were performed with Stata MP (version 17.0).

6.12 MONITORING

The Data Monitoring Committee (DMC) will carry out monthly scheduling monitoring visits, at least every ten participants. Participant rights and well-being protection, trial data accuracy and trial conduction will be verified to be in compliance with the currently approved protocol. An interim-analysis will be performed by SS when 50% of patients (n=24) have been randomised and have completed the follow-up. Promotor and PI agreement will end the trial only if there will be participant harm proof, prematured statistical significance, futility, logistical issues.

All medicines will be administered according to the usual clinical practice of the ARTD Service, TOC Service and the AEMPS technical sheet (28,29,38–41,30–37).

In this clinical trial, there is no medication that is not allowed.

The container of the research drug will be labeled, and at the time of use the patient number and date of use will be indicated on the label, and it will be kept for later accounting. In this way, the traceability of the medication and therapeutic compliance will be ensured.

In addition, each participant will be provided with an Anesthesia Assessment Sheet where all medication administered during the perioperative period will be listed. This document is individualized and stored in the PMR.

The PI and sponsor of this clinical trial will not make any deviation or modification to the protocol without the permission, prior review and written opinion in favour of the modification from the AEMPS and CEICA.

All deviations from the original statistical plan will be described and duly justified in writing in the new version of the protocol and/or in the final report of the clinical trial, if necessary.

6.13 HARMS

Adverse Events (AE), Serious Adverse Events (SAE), Adverse Drug Reactions (ADR), Serious Adverse Drug Reactions (SADR) and Unexpected Adverse Drug Reactions (UADR) will be defined according to Guideline for good clinical practice of European Medicines Agency (55). According to AEMPS Levobupivacaine label, common adverse reactions (AR) are hypotension, nausea, vomiting, anemia, dizziness, cephalea, fever, etc (23). IRP will determine relatedness of an event to drug based on a temporal relationship, unexpected or unexplained nature, previous medical conditions or concomitant medications. Every AE, SAE, ADR, SADR and UADR will be recorded in the DCF and the PMC. They will be notified, in a specific record form, to sponsor and health authorities within 24 hours of first knowledge by PI. They will be followed until they will be cronic or cured.

For secondary outcomes, harm variables will be recorded at operating room, 4-hour, 24-hour and 30-day after intervention eg IBPB, anesthetics, PACU and hospital complications and mortality. 30-day after review will consider potential long-term intervention complications.

7 ETHICS AND DISSEMINATION

This study has been approved by the *Ethics Committee* of Clinical Research of Aragon (CEICA; Approval registration: EC19/093), the Institutional review board of HUMS (Spain) and the study sponsor (*Aragon Institute* for Health *Research [*IISAragon]). This trial will be conducted in compliance with the European Union Clinical Trials Directive (2001/20/EC), the principles of the Declaration of Helsinki (2013) and Spanish Organic Law of 3/2018 on Personal data protection and guarantee of digital rights (56–58). *Ethics Committee* of Clinical Research of Aragon (CEICA; Approval registration: EC19/093) approved the non-substacial modification of the study protocol to include a secondary cost-analysis on 10th February 2021 (Ethics approval document is uploaded at the end of this file).

A written informed consent (IC) with impartial witness will be obtained from all subjects by PI and RRP after hospital admission. By signing IC, participants agree with the storage of data and publication of the study result.

All the material used is obtained thanks to the HUMS (Zaragoza, Spain). The knowledge derived from this study can generate future commercial benefits that will belong to the research team. Participants will not be entitled to claim part of that benefit. No economic compensation will be made to the patients included in the research work.

The diagnostic tests derived from this research project have no relevance for the health of the participants or their families. No genetic analysis is performed in this work.

In this research work, the participation of students is not required.

The outcomes of this clinical trial will become a property of the Department of Anesthesia who will decide the publication policy. The conclusions will lead to a PhD research work from the Doctoral School of the University of Zaragoza, will be presented at congresses and in scientific publications but will always be done with grouped data and no participant could be identified. As the article 42 of the Spanish Law RD 1090/2015 defines, the results obtained in the clinical trial will be published, whatever their result, in scientific journals with mention to the Ethics Committee that approved the study. Likewise, the promoter will publish the report of results once the clinical trial will be concluded, according to article 47 of the mentioned law.

The study civil responsibility insurance (Berkley, Assurance number: 2034180) is available in accordance with current Spanish legislation (Royal Decree 1090/2015).

The authors declare that they have no competing interests.

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9 ANEXO: Additional analysis of the study REDOLEV-2019

After a narrative review of the literature on the cost analysis of brachial plexus block with interscalene approach (BPBAI), we obtained only three results. Gonano et al (2009) concluded that BPBAI is a more efficient technique compared to general anesthesia for arthroscopic shoulder surgery (59). However, no cost studies comparing different regional anesthesia techniques in this type of surgery have been reported.

Therefore, we proposed a non-substantial modification to the Protocol v1.0 of the REDOLEV-2019 Study, approved on December 18, 2019 (EC19/093) by the Spanish Agency of Medicines and Health Products (AEMPS) and the Research Ethics Committee of the Autonomous Community of Aragon (CEICA). Thus, *Ethics Committee* of Clinical Research of Aragon (CEICA) approved the non-substacial modification of the study protocol to include a secondary cost-analysis on 10th February 2021 (Ethics approval document is uploaded at the Clinicaltrials.gov).