Comparison of Diaphragmatic Paralysis, Respiratory Function and Postoperative Pain After Interscalene Brachial Plexus Block With a Reduction Dose of Levobupivacaine 0.25% 10 ml Versus 20 ml Undergoing Arthroscopic Shoulder Surgery: Study Protocol for the Randomized, Controlled and Double-blinded REDOLEV Study.

Pablo Oliver-Fornies (✉ pablo.oliver.fornies@gmail.com)

Hospital Clínico Universitario Lozano Blesa <https://orcid.org/0000-0001-7483-4807>

Pablo Ortega Lahuerta

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Roberto Gomez Gomez

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Inmaculada Gonzalo Pellicer

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Leticia Oliden Gutierrez

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Jose Vinuales Cabeza

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Lucia Gallego Ligorit

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Carlos Edgardo Orellana Melgar

Miguel Servet University Hospital: Hospital Universitario Miguel Servet

Study protocol

Keywords: Diaphragmatic Paralysis, Interscalene Brachial Plexus Block, Ultrasound, Spirometry, Postoperative pain, Arthroscopic shoulder surgery

Posted Date: December 16th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-128424/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Trials on April 19th, 2021. See the published version at <https://doi.org/10.1186/s13063-021-05216-6>.

Abstract

Background: Arthroscopic shoulder surgery involves dynamic and severe postoperative pain. Interscalene brachial plexus block provides adequate analgesia, but the spread of local anaesthetics administered causes a phrenic nerve block that entrains a nonnegligible incidence of hemidiaphragmatic paralysis acute.

The main objective of this trial is to compare the hemidiaphragmatic paralysis after interscalene brachial plexus block in arthroscopic shoulder surgery, between a standard volume (20 ml) and a low volume (10 ml) of 0.25% levobupivacaine.

Methods: This is a comparative, prospective, single-center, double-blind, two-arm randomized controlled trial. Forty-eight patients will be included. The primary end-point is to determine the hemidiaphragmatic paralysis incidence diagnosed by the diaphragmatic thickness ratio in ultrasound. The secondary endpoints are as follows: (1) hemidiaphragmatic paralysis incidence diagnosed by forced vital capacity and (2) forced expiratory volume at 1 second decrease in spirometry; (3) hemidiaphragmatic paralysis incidence diagnosed by using diaphragmatic excursion decrease in ultrasound; (4) postoperative pain regarding 24-hour morphine intravenous total consumption and (5) time to first analgesic consumption of patient-controlled analgesia pump; and (6) postoperative harm between the two trial arms.

Discussion: This trial would demonstrate that low-volume interscalene brachial plexus block decreases hemidiaphragmatic paralysis in arthroscopic shoulder surgery by using spirometry and ultrasound and would not provide inferior postoperative analgesia according to opioid requirements of postoperative patient-controlled analgesia in comparison to the standard volume used in current practice.

Trial registration: EudraCT and Spanish Trial Register (REec) registration number: 2019-003855-12 (Registered on 07 January 2020). ClinicalTrials.gov identification number: NCT04385966 (Retrospectively registered on 08 May 2020). *Ethics Committee* approval: EC19/093 (18 Dic 2019).

Introduction

Background and rationale {6a}

Arthroscopic shoulder surgery involves severe and dynamic postoperative pain, which can compromise early patient rehabilitation. Clinical practice guidelines recommend a multimodal analgesic regimen including regional analgesic techniques such as the interscalene brachial plexus block (IBPB: ICD-10 code 3E0T3CZ) in this surgery (1, 2). IBPB offers adequate postoperative analgesia, low incidence of nausea and vomiting and low opioid requirements. However, it could also result in severe complications such as phrenic block (1). In 1991, Urmeý et al. determined that IBPB produces 100% phrenic blockade with ipsilateral hemidiaphragmatic paralysis acute (HDPa), which decreases pulmonary function (ICD-10 code: J98.6) (2–5). Thanks to ultrasound (US), local anaesthetics (LA) doses required in IBPB could have been reduced. Recent publications have proven that HDPa incidence has been reduced to 10–26% (6–9).

This diaphragmatic dysfunction could be detected in spirometry as a decrease in forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV1) by using US, which has become a main diagnostic tool in thorax assessment (10).

Classically, IBPB performance is contraindicated in patients with decreased pulmonary function (3). Some publications have tried to find a safe low LA dose of IBPB that could decrease postoperative harm and others to compare IBPB to other regional anaesthetic techniques, but HDPA still remains a major concern. More randomized trials are therefore needed to perform IBPB with lower LA doses in comparison to current publications.

In this article, we will describe the study design and protocol of the REDOLEV-2019 Study (Reduction DOse of LEVobupivacaine Study), which is a randomized and controlled comparison designed to determine the HDPA between a standard volume versus a low volume in patients after IBPB for arthroscopic shoulder surgery in current anaesthesiologist practice. We hypothesized that reducing the volume of 0.25% levobupivacaine from standard volume (20 ml) to low volume (10 ml) may decrease the incidence of HDPA in US and in spirometry and would not be inferior in terms of postoperative pain and harm after IBPB in arthroscopic shoulder surgery.

Objectives {7}

The primary objective is to determine the HDPA incidence using 10 ml versus 20 ml of 0.25% levobupivacaine for IBPB in patients undergoing arthroscopic shoulder surgery according to DTR in US.

The secondary study objectives are to compare the incidence of HDPA, postoperative pain and harm after 10 ml versus 20 ml of 0.25% levobupivacaine IBPB in patients undergoing arthroscopic shoulder surgery.

Trial design {8}

The REDOLEV-2019 trial is designed as a randomized, comparative, prospective, phase III, single-center, double-blind, two-arm and controlled clinical trial (RCT). This design is reported in accordance with to the Consolidated Standards of Reporting Trials (CONSORT) and the SPIRIT statements: additional files consist in the (1) SPIRIT checklist protocol and (2) the SPIRIT diagram of the study participant timeline (11, 12). Forty-eight patients programmed for arthroscopic shoulder surgery under general anaesthesia (GA) with IBPB will be included. Eligible patients will be randomly allocated to 2 groups: Group Control (G1) with a standard volume IBPB (20 ml of 0.25% levobupivacaine) or Group Treatment (G2) with a low volume IBPB (10 ml of 0.25% levobupivacaine). Figure 1 is the trial flowchart.

Methods: Participants, Interventions And Outcomes

This trial will be conducted in compliance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013) (13,14).

Study setting {9}

Participants will be only recruited from the Shoulder Surgery Division and Regional Anaesthesia Division of the HUMS in Zaragoza, Spain.

Eligibility criteria {10}

Eligible patients must comply with the following inclusion criteria at randomization: (1) aged from 18 to 80 years; (2) ASA I-III; and (3) scheduled for arthroscopic shoulder surgery and interscalene brachial plexus block. The exclusion criteria will be as follows: (1) age <18 and >80 years; (2) pregnancy; (3) exclusion to perform IBPB or spirometry; (4) diagnosis of allergy to amide type LA, opioids or non-steroidal anti-inflammatory drugs; (5) background of pulmonary disease (moderate or severe chronic obstructive pulmonary disease or severe asthma), diaphragmatic paralysis or neuromuscular disease or brachial neuropathy; (6) coagulation disorder; and (7) chronic opioid consumption: >3 months or oral morphine equivalent to >5 mg per day for a month.

Who will take informed consent? {26a}

Written informed consent (IC) with impartial witnesses will be obtained from all participants by PI after hospital admission.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

By signing IC, participants agree with the storage of data and publication of the results in the main and ancillary studies.

Interventions

Explanation for the choice of comparators {6b}

A review of the literature showed that volume and concentration regimens of LA greater than 10 ml and 0.25% still reach a high incidence of HDPA (15–17). Therefore, this study used a low volume (10 ml levobupivacaine 0.25%: 25 mg), which has been shown to offer adequate postoperative analgesia. As a comparator, this study includes the current clinical dose of IBPB (20 ml levobupivacaine 0.25%: 50 mg) usually used in our hospital. The safety of levobupivacaine is well known (18).

Intervention description {11a}

Eligible participants will be randomized in equal proportions between two study groups receiving either treatment only once as a single-shot IBPB before surgery.

During the hospital stay, there will be three visits to the participants. Spirometry and US will be performed as baseline and 4-hour and 24-hour postoperative assessments. After post-anaesthesia care unit (PACU) entry, a morphine IV PCA pump will be administered.

The interventions will be entirely integrated within routine clinical practice.

Interscalene brachial plexus block (IBPB) will be guided by US with a linear transducer (GE Medical, Milwaukee, WI, USA). Then, skin sterilization, an in-plane approach with a 22-gauge 50 mm Stimuplex® Ultra 360° needle, will be used to deposit the study LA in the interscalene space at the level of the C5-C6 vertebra. This will be a conventional IBPB approach as described by Winnie (19). Before surgery, IBPB success will be determined using a sensory test in the fingers. Evidence of block failure after 15 minutes will exclude the case from analysis.

Diaphragmatic US will be performed before (baseline) and 4 hours (1 hour minimum after extubation) after IBPB in a sitting and supine position. Ipsilateral and contralateral hemidiaphragms will be assessed using a linear US transducer (GE Medical, Milwaukee, WI, USA). The US apposition zone will be assessed in the anterior axillary line, and the diaphragmatic thickness will be recorded for the maximal inspiration (inspiratory diaphragmatic thickness; IDT) and expiratory (expiratory diaphragmatic thickness; EDT) values. Their ratio will be expressed as the DTR. ED will be assessed on maximal inspiration and expiration as the number of intercostal spaces and motion type, expressed by normal/caudal, null or cephalic/paradoxical motion of the diaphragm with inspiration.

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 the sitting and supine positions. 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) (20–22). FVC, FEV1, FEV1/FVC ratio and peak expiratory flow (PEF) will be measured three times every assessment to comply with acceptable and reproducible criteria. The best FVC and FEV1 effort will be recorded.

Combined Regional-General Anaesthesia: Before induction, IBPB will be developed in the surgery theatre. Antibiotic prophylaxis will be given IV. All patients will receive an IV GA with fentanyl 2 µg.kg⁻¹, propofol 2 mg.kg⁻¹ and rocuronium 0.6 mg.kg⁻¹ before being orotracheally intubated. Mechanical ventilation will be performed with a respiratory rate and tidal volume adjusted to maintain normocapnia. The bispectral index (BIS) and train of four (ToF) will be monitored. Anaesthesia will be maintained with sevoflurane (0.7-1 MAC) to obtain a 40-60 BIS monitor. Intraoperative analgesia with remifentanyl IV (0.05–0.2 µg.min.kg⁻¹) will be administered. 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. Fluid management with balanced crystalloids is aimed at normovolemia. Before extubation, ToF 4/4 <90% Sugammadex 2 mg.kg⁻¹ will be used. After leaving the surgery theatre, the patient will attend to the PACU.

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

A postoperative patient-controlled analgesia pump (CADD®-Solis Infusion System, Smiths Medical, Minneapolis; USA) of morphine IV will be administered from PACU entry until 24-hour postoperative

follow-up. The PCA pump will be delivered a 1 mg bolus (2 ml) with a 10-minute time-close without basal IV administration. Every participant's numeric rating scale (NRS) pain score (0-10) will be recorded in the PACU and at 24 hours.

PACU Interventions: The second US and spirometry will be performed. Participants will be quit from the PACU after accomplishing an Aldrette score greater than 8 of 10.

Hospital Interventions: During hospitalization, all patients will receive 1 g paracetamol and 50 mg enantyum IV alternatively every 4 hours. Metamizol IV (2 g) will be given to participants with a non-steroidal anti-inflammatory drug allergic background. Ondansetron IV (4 mg) every 12 hours will be given as nausea and vomiting prophylaxis. After 24 hours of follow-up, the NRS score will be recorded. The follow-up will finish 30 days postoperatively after checking the incidence, frequency and severity of serious adverse events and hospital admission reviews.

Criteria for discontinuing or modifying allocated interventions {11b}

The main study intervention will be a single-shot IBPB, so once it was performed the intervention cannot be discontinued or modified.

Strategies to improve adherence to interventions {11c}

Before study intervention, every participant will be trained in spirometry performance and PCA management. Every study drugs will be provided and relabelled by the Pharmacy Department of HUMS. After recruitment, they will be checked and destroyed as current practice according to *Ethics Committee* of Clinical Research of Aragon (CEICA) guidelines.

Relevant concomitant care permitted or prohibited during the trial {11d}

Only analgesia allowed in the protocol will be administered to the participants.

Provisions for post-trial care {30}

The study interventions are current anaesthesia practice so no provision or compensation will be given.

Outcomes {12}

The primary outcome of the REDOLEV-2019 trial is the incidence of HDPa according to DTR in US between the two trial groups. HDPa after IBPB will be diagnosed with a DTR<1.2 (23,24).

Secondary study outcomes are as follows: (1) the incidence of HDPa diagnosed in spirometry by using a diminution of $\geq 20\%$ of baseline, 4-hour and 24-hour postoperative FCV and (2) FEV₁; (3) the incidence of HDPa according to DE in US expressed by number of intercostal spaces (reduction $\geq 25\%$) and motion type (positive to paradoxical or null diaphragmatic motion); (4) postoperative 24-hour cumulative IV morphine consumption (mg) and (5) time to first analgesic consumption (min) of PCA pump; and (6) the

incidence, frequency and severity of (serious) adverse events as established by CTCAE v4.0 (25). Every secondary outcome will be compared in each study group. This is a per intention-to-treat study.

Participant timeline {13}

The schedule diagram of participant timeline is shown in Table 1.

Table 1.

Participant Timeline of REDOLEV-2019 Clinical Trial.

STUDY PERIOD						
	Enrolment	IBPB	Post-allocation			Close-out
TIMEPOINT	<i>Before surgery</i>	0	3h	4h	24h	30 days
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Medical background	X					
Random Allocation	X					
INTERVENTIONS:						
<i>G1: IBPB 20 ml</i>		X				
<i>G2: IBPB 10 ml</i>		X				
ASSESSMENTS:						
US: DTR, ED(n°esp) and ED(type)	X			X	X	
Spirometry (FVC and FEV1)	X			X		
Pain: 24hTotal Consumption and Time to first.				X	X	
Harms				X	X	X

This template is copyrighted by the SPIRIT Group. Abbreviations: DE, Diaphragmatic excursion; DTR, Diaphragmatic Thickness Ratio; FCV, Forced vital capacity; FEV1, Forced expiratory volume at 1 second; IBPB, Interscalene brachial plexus block.

Sample size {14}

This trial assumed an HDPa after IBPB rate between 90% (control group) and 33% (treatment group) according to previous studies (6,15,26). These findings suggest that after decreasing the IBPB LA dose

(10 ml, 0.25% or 25 mg), we expect to find less HDPa after IBPB.

Therefore, to power this trial to identify a mean difference of 90%-33% with a two-sided significance level of 1% and power of 90% with same allocation to two arms will demand 21 patients in each trial arm. Assuming a 10% dropout rate, 24 will be enrolled per arm, i.e., 48 participants will be the total sample size, as calculated using Epidat® software (27,28).

Recruitment {15}

HUMS provides health care to a population of more than 350000 inhabitants, mostly urban. An average of 100 arthroscopic shoulder surgeries is performed every year. Enrolment began in February 2020 before the coronavirus disease 2019 (COVID-19) pandemic and is anticipated to continue through 2021.

Prospective participants of the surgery waiting list will be screened by reviewing health records to determine eligibility. Inclusion and exclusion criteria will be assessed. Patients will be recruited after hospital admission hours before surgery. The baseline evaluation will include a common assessment battery, baseline spirometry and US. After the COVID-19 outbreak in March, all participants to be enrolled must have a reverse-transcription polymerase chain reaction (PCR) test with a negative result for COVID-19. A COVID-19 triage questionnaire recommended by the European Respiratory Society (ERS) will be completed (29). This trial will comply with every recommendation of ERS and SEPAR for lung function testing (29,30).

Assignment of interventions: allocation

Sequence generation {16a}

In this trial, four research teams will participate: IBPB research physicians (IRPs), assessment research physicians (ARPs), recruitment research physicians (RRPs) and statistical staff (SS). The allocation sequence as per a random number table has been generated using Epidat® software by statistical staff.

Concealment mechanism {16b}

IRP will randomly allocate every patient and will carry out the IBPB and the administration of the study drug. IRP will be a group of four nonblinded attending anaesthesiologists experienced in regional blocks.

Implementation {16c}

During enrolment, RRP will consecutively include every participant. When IC has been obtained, ARP will conduct every spirometry (a blinded pneumologist) and every US assessment (a blinded anaesthesiologist). After recruitment will finish, statistical staff will conduct the study analyses

Assignment of interventions: Blinding

Who will be blinded {17a}

Due to the study intervention, IRP will be the only non-blinded research physician. They will be in charge of randomization and will guard the randomization list, which will include a randomization number and a participant study code. The ARP who will be responsible for US and spirometry assessments, the RRP, the care providers and the trial participants will be kept blinded until after 24-hour postoperative follow-up.

Procedure for unblinding if needed {17b}

As mentioned before, the IRP in charge of IBPB cannot be blinded for the treatment allocation. Consequently, a code break is not necessary. If emergencies happen, they will be managed by unblinded IRPs.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All outcome variables will be collected in the DCF, and duplicated in the participant medical record by RRP and ARP. As the primary outcome, HDPA will be observed by using DTR in US, which provides 93% sensitivity and 100% specificity (23). Superior to 95% inter-observer and intra-observer reproducibility of diaphragmatic motion has been reported (31). Every participant will be evaluated at baseline and after IBPB on 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 90% sensitivity and 97% specificity (32,33). It will be performed in the supine and sitting positions to increase the sensitivity and specificity (34). Postoperative pain will be measured and collected by using a PCA pump record. PCA provides a better pain management and increases the patient satisfaction score (35). The incidence, frequency and severity of adverse events, as assessed by CTCAE v4.0, will be recorded (25).

Every investigator will be trained in the study interventions. The ARP anaesthesiologist has been training in diaphragmatic US for six months in advance.

Plans to promote participant retention and complete follow-up {18b}

Participants may withdraw from the study for any reason. The PI may retire patients to assure their safety. Withdrawal reasons will be asked, measured and figured in the DCF.

Data management {19}

All data will be hosted electronically on the HUMS network, protected by a firewall. Participant study data will be stored for 25 years at the participating site. See Appendix 1 for further information.

Confidentiality {27}

This study will be conducted in compliance with the Spanish Organic Law of 3/2018 on Personal data protection and guarantee of digital rights (36).

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Excel (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 $p < 0.02$. The Bonferroni method will be applied to adjust the overall level of significance for the primary and secondary outcomes.

A descriptive data analysis will be carried out: qualitative variables (sex, surgical side, BPBAI complications, etc.) will be presented using the frequency distribution of the percentages, and the quantitative variables studied (US and spirometer variables, etc.) will be assessed 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, statistical methods will be carried out. 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 Martinez-González et al. (37,38). Concerning bivariate analysis or comparison between two variables (factors), the association between the factors will be investigated using hypothesis contrasting tests. A comparison of proportions with chi-square or Fisher's exact test will be carried out if both variables compared were qualitative. If one of them was quantitative, a comparison of means will be performed applying Student's t-test and ANOVA; if they do not follow a normal distribution, the Mann-Whitney U-test or the Kruskal-Wallis test will be performed. 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 (Student's t-test, ANOVA for repeated measurements), and if they do not follow a normal distribution, the Wilcoxon test or the Friedman test will be performed.

Interim analyses {21b}

An interim analysis will be performed by SS when half of the participants ($n=24$) have been randomized and have completed the follow-up.

Methods for additional analyses (e.g. subgroup analyses) {20b}

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.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

This is a per intention-to-treat study.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

See **Appendix 1**.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The focus of the visit monitoring will be to verify the source documents and adverse events reports. Source documents are defined as DCF, participant medical charts, associated reports and assessment records. Process will be independent from investigators.

Composition of the data monitoring committee, its role and reporting structure {21a}

Adverse events, serious adverse events, adverse drug reactions, unexpected adverse drug reactions and serious adverse drug reactions will be defined according to the guidelines for good clinical practice of the European Medicines Agency (39). Levobupivacaine profile is described by the Spanish Agency of Medicines and Medical Devices (AEMPS) (18). IRP will determine the relatedness of an incident to the study drug depending on previous medical conditions, concomitant medications, temporal relationships and unexpected or unexplained nature.

Adverse event reporting and harms {22}

Every adverse event or reaction will be recorded in the DCF and the participant medical record. They will be followed until they will be determined to be chronic or cured.

For secondary outcomes, harmful variables will be recorded in the operating room, 4 hours, 24 hours and 30 days after IBPB.

Frequency and plans for auditing trial conduct {23}

Monitoring visits will be scheduled monthly, at least every ten participants.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Protocol modifications, SAE and other unintended effects of trial interventions or trial conduct will be collecting in the DCF and participant medical record. They will assess properly and manage by the PI and the responsible anesthesiologist. They will be reported to the promotor, Ethics Committee and AEMPS.

Dissemination plans {31a}

Trial outcomes will be published in (inter)national journals, communicated to anesthesiologist associations, presented at (inter)national congresses and released to the participating physicians and participants.

Discussion

Performing an IBPB in patients with respiratory background results in a challenge to anaesthesiologists: to set the fewest possible LA doses to decrease secondary effects or to assure postoperative analgesia despite postoperative respiratory complications. Here, quantity is not always synonymous with quality. US can significantly contribute to this goal by improving plexus brachial image but does not always assure phrenic block prevention. The current literature suggests that IBPB experience improves HDPa prevention, but the safe dose of IBPB remains uncertain.

In healthy patients, HDPa is usually well tolerated, but in cases of a severe respiratory background, HDPa cannot be afforded, and IBPB is contraindicated. Supraclavicular, suprascapular or superior trunk blocks have been studied as an alternative to IBPB in arthroscopic shoulder surgery (40–43). Although supraclavicular block is considered an acceptable choice and clinically similar to IBPB, its incidence of HDPa is still up to 59%(44). Otherwise, superior trunk block has recently achieved similar analgesia, but HDPa secondary may reach a high incidence of 76% (40). Any regional block has already prevented phrenic nerve block, assuring adequate postoperative analgesia. Therefore, IBPB is still considered the first-choice regional block recommended in shoulder surgery (1).

Regarding the literature, few studies have assessed IBPB performance in arthroscopic shoulder surgery by simultaneously determining the three main IBPB features: diaphragmatic motion, respiratory function and postoperative analgesia (6, 9, 15). This is the first RCT in our country to measure them all quantitatively using DTR, spirometry and PCA analgesia (45). To date, similar works have proposed high volume and concentration LA doses in IBPB in comparison to our current practice (15–17). This study will compare one of the smallest volumes used in the literature (15, 17, 46–48).

The methodology will try to increase the accuracy of HDPa diagnosis by including three independent assessments (US, spirometry and pain). US assessment will include two different measures, DTR and DE. Every US and spirometric assessment will be measured in the sitting and supine positions to assess the position influence on diaphragmatic dysfunction (10, 34, 49). Moreover, every participant will be his own case-control comparison by assessing both diaphragm sides, the phrenic blocked side and the contralateral side, to assess the contralateral diaphragmatic motion. Therefore, our objective is to document and analyse every benefit and risk of IBPB together in decreasing any confounding factor influences.

A few years ago, chest X-ray and spirometry were the only two tools for diagnosing HDPa (3–5). In the 1990s, US was introduced, and the first diagnostic criteria, such as the diaphragm thickening fraction, were described(50). Currently, the role of US in the diagnosis of HDPa has emerged. B-Mode US could assess HDPa with 93% sensitivity and 100% specificity (23). Inspiratory and expiratory diaphragmatic

thicknesses have been measured to study extubation prediction, chronic phrenic paralysis and pulmonary diseases. Here, they will be used in an RCT to compare the HDPa after IBPB for the first time (45). Diaphragmatic dysfunction has been usually diagnosed only to measure diaphragmatic excursion with a dichotomous outcome (i.e., positive, null or paradoxical) (6, 15, 26, 51). Postoperative analgesia has usually been assessed by a satisfaction scale or prescribed analgesic consumption (51). This study will add a quantitative analysis of postoperative analgesia by using a PCA pump with only bolus dose to minimize the external influences in pain management and not influence respiratory function. The study interventions are non-invasive, painless, non-radiation, reproductive, well-tolerated and free of known adverse side effects. The only pharmacological intervention required will be performed as current practice. Therefore, the study benefits would be greater than the possible study harms associated.

In summary, our outcomes will contribute to the growing evidence database for decreasing IBPB LA doses to obtain an IBPB with a nonsignificant HDPa incidence. If the primary and secondary study hypotheses are supported, these findings will provide a safe volume to perform IBPB with adequate postoperative analgesia that would improve anaesthetic management in arthroscopic shoulder surgery. Additionally, the study findings will provide critical information regarding patients with respiratory backgrounds undergoing upper extremity surgery, in which IBPB is forbidden. Therefore, these patients could benefit from a low volume IBPB, avoiding a GA that they had been forced to undergo (6, 16, 17, 45). Briefly, this study could help to reconsider the future contraindications of IBPB and modify the current anaesthesiologist practice based on the evidence.

Trial status

The study is currently in the process of recruiting participants. Recruitment commenced on 11 February 2020, was stopped due to COVID outbreak and will be finished in 2021. This article is based on protocol version 1.0 (17 October 2019).

Abbreviations

ARP, Assessment research physician; CEICA, *Ethics Committee* of Clinical Research of Aragon; DCF, Data Collection Form; DE, Diaphragmatic excursion; DTR, Diaphragmatic Thickness Ratio; EDT, Expiratory Diaphragmatic Thickness; FCV, Forced vital capacity; FEV1, Forced expiratory volume at 1 second; GA, General Anaesthesia; HDPa, Hemidiaphragmatic Paralysis Acute; HUMS, Hospital Universitario Miguel Servet; IBPB, Interscalene Brachial Plexus Block; IC, Informed Consent; IDT, Inspiratory Diaphragmatic Thickness; IRP, IBPB research physicians; LA, Local anaesthetic; NRS, Numerical Rating Scale; PACU, Post-Anesthesia Care Unit; PCA, Patient-Controlled Analgesia; PI, Principal Investigator; RCT, Randomized Controlled Trial; RP, Research Physician; RRP, Recruitment research physicians; SS, Statistical staff; US, Ultrasound.

Declarations

Acknowledgements

The authors want to acknowledge the support of Daniel Bordolaba (Department of Statistics of Aragon Health Sciences Institute [IACS]), P. Millan and C. Torrubia (Aragon Institute for Health Research [IISAragon] monitors) with the statistical analysis, study design and monitoring. Also, we would like to thank the effort of R. Carbonell, Y. Duran, F. Carbo, F. Jimenez, A. Lucas, B. Perez, L. Tardos, O. Urbano and Alvaro Navarro Rodriguez-Villanueva for their help in conducting the study.

Authors' contributions {31b}

POF: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing-Original Draft, Visualization and Project administration. **JPOL, RGG and IGP:** Investigation, Resources, Supervision. **JVC:** Conceptualization and Writing-Review&Editing. **COM:** Investigation, Resources and Data curation. **LGL:** Methodology, Software, Formal analysis and Writing-Review&Editing. All authors read and approved the final manuscript.

Funding {4}

This is investigator-initiated research with no source of funding.

Availability of data and materials {29}

See **Appendix 1**.

Ethics approval and consent to participate {24}

This study has been approved by the *Ethics Committee* of Clinical Research of Aragon (CEICA; Approval registration: EC19/093; Date 18 December 2019; Approval responsible: Maria Gonzalez Hinojos, Ethics Committee Secretary). Written, informed consent to participate will be obtained from all participants.

Consent for publication {32}

Informed consent will be available at <https://clinicaltrials.gov/ct2/show/NCT04385966>.

Competing interests {28}

The authors declare that they have no competing interests.

References

1. Toma O, Persoons B, Pogatzki-Zahn E, Van de Velde M, Joshi GP, Schug S, et al. PROSPECT guideline for rotator cuff repair surgery: systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia*. 2019;74(10):1320–31.

2. De España G, Internacional C. Clasificación Internacional de Enfermedades. 10ª Revisión. 10ª. Ministerio de Sanidad C y B social. G de E, editor. Vol. 1. Madrid: Ministerio de Sanidad, Consumo y Bienestar social. Gobierno de España; 2018. 1492 p.
3. Urmeý WF, Talts KH, Sharrock NE. One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. *Anesth Analg.* 1991;72(4):498–503.
4. Urmeý WF, McDonald M. Hemidiaphragmatic Paresis During Interscalene Brachial Plexus Block: Effects on Pulmonary Function and Chest Wall Mechanics. *Anesth Analg.* 1992;74(3):352–7.
5. Urmeý WF, Gloeggler P. Pulmonary Function Changes During Interscalene Brachial Plexus Block: Effects of Decreasing Local Anesthetic Injection Volume. *Reg Anesth.* 1993;18:244–9.
6. Thackeray EM, Swenson JD, Gertsch MC, Phillips KM, Steele JW, Burks RT, et al. Diaphragm function after interscalene brachial plexus block: A double-blind, randomized comparison of 0.25% and 0.125% bupivacaine. *J Shoulder Elb Surg.* 2013;22(3):381–6.
7. Palhais N, Brull R, Kern C, Jacot-Guillarmod A, Charmoy A, Farron A, et al. Extrafascial injection for interscalene brachial plexus block reduces respiratory complications compared with a conventional intrafascial injection: A randomized, controlled, double-blind trial. *Br J Anaesth.* 2016;116(4):531–7.
8. Nakamura T, Miyamoto S, Aishin K HM. Levobupivacaine for Ultrasound-guided Interscalene Block: Block with 6 ml Leads to Less Occurrence of Respiratory Depression and Hemidiaphragmatic Paralysis. *Masui.* 2015;64(7):756–60.
9. Stundner O, Meissnitzer M, Brummett CM, Moser S, Forstner R, Koköfer A, et al. Comparison of tissue distribution , phrenic nerve involvement , and epidural spread in standard- vs low-volume ultrasound-guided interscalene plexus block using contrast magnetic resonance imaging : a randomized , controlled trial †. *Br J Anaesth.* 2016;116(3):405–12.
10. Boon AJ, Gorman CO. Ultrasound in the Assessment of Respiration. *J Clin Neurophysiol.* 2016;33(2):112–9.
11. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *Int J Surg.* 2012;10(1):28–55.
12. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013;346:1–42.
13. European Parliament. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in th. *Man Res Ethics Committees.* 2010;(April 2001):184–95.
14. Asociación Médica Mundial. Declaración de Helsinki de la Asociacion Medica Mundial – Principios éticos para las investigaciones médicas en seres humanos [Internet]. Vol. 81, wma. 2013 [cited 2020 Jan 27]. p. 1–5. Available from: <https://www.wma.net/es/polices-post/declaracion-de-helsinki-de-la-amm-principios-eticos-para-las-investigaciones-medicas-en-seres-humanos/>

15. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJL. Effect of local anaesthetic volume (20 vs 5 ml) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *Br J Anaesth*. 2008;101(4):549–56.
16. Sinha SK, Abrams JH, Barnett JT, Muller JG, Lahiri B, Bernstein BA, et al. Decreasing the local anesthetic volume from 20 to 10 mL for ultrasound-guided interscalene block at the cricoid level does not reduce the incidence of hemidiaphragmatic paresis. *Reg Anesth Pain Med*. 2011;36(1):17–20.
17. Marty P, Ferré F, Basset B, Marquis C, Bataille B, Chaubard M, et al. Diaphragmatic paralysis in obese patients in arthroscopic shoulder surgery: consequences and causes [Internet]. *Journal of Anesthesia*. Springer Japan; 2018 [cited 2018 Apr 15]. p. 1–8. Available from: <http://link.springer.com/10.1007/s00540-018-2477-9>
18. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica: Chirocane 2,5 mg/ml Solución inyectable y para perfusión [Internet]. CIMA. 2000 [cited 2019 May 7]. p. 1–13. Available from: https://cima.aemps.es/cima/pdfs/es/ft/63171/63171_ft.pdf
19. Winnie A. Interscalene brachial plexus block. *Anesth Analg*. 1970;49:455–66.
20. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. American Thoracic Society Documents: Recommendations for a Standardized Pulmonary Function Report An Of fi cial American Thoracic Society Technical Statement. *Am J Respir Crit Care Med*. 2017;196(11):1463–72.
21. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):E70–88.
22. García-río F, Calle M, Burgos F, Casan P, Galdiz JB, Giner J, et al. Espirometría: Normativa SEPAR. *Arch Bronconeumol*. 2013;49(9):388–401.
23. Boon AJ, Sekiguchi H, Harper CJ, Strommen JA, Ghahfarokhi LS, Watson JC, et al. Sensitivity and specificity of diagnostic ultrasound in the diagnosis of phrenic neuropathy. *Neurology*. 2014;83(14):1264–70.
24. Sociedad Española de Neumología y Aparato Respiratorio. Manual SEPAR de procedimientos. Ecografía torácica. Respira E, editor. Vol. 33, Manual Separ De Procedimientos. SEPAR; 2017. 1–112 p.
25. U.S.Department of Health and Hhuman Services. Common Terminology Criteria for Adverse Events v4.0. NIH Publ. 2009;2009:0–71.
26. Aliste J, Bravo D, Finlayson RJ, Tran DQ. A randomized comparison between interscalene and combined infraclavicular-suprascapular blocks for arthroscopic shoulder surgeryComparaison randomisée entre le bloc interscalénique et le bloc combiné infraclaviculaire et suprascapulaire pour une chirurgie. *Can J Anesth Can d’anesthésie*. 2017;65(3):280–7.
27. Conselleira de Salud. Servizo Galego de Saúde. Xunta de Galicia. Manual de ayuda: Muestreo [Internet]. Servizo Galego de Saúde. 2018 [cited 2019 Mar 3]. p. 48. Available from: <https://www.sergas.es/Saude-publica/Documents/1931/3-Ayuda Muestreo.pdf>

28. Santiago Pérez MI, Castillo Salgado C, Hervada Vidal X, Silva Ayçaguer LC, Loyola Elizondo E, Vázquez Fernández E. Epidat 3.0 programa para análisis epidemiológico de datos tabulados. *Rev Esp Salud Publica*. 2007;78(2):277–80.
29. European Respiratory Society. Recommendation from ERS Group 9.1 (Respiratory function technologists /Scientists) Lung function testing during COVID-19 pandemic and beyond. Vol. 1. 2020.
30. Guerra A, Torralba García Y, Diaz-Perez D, Angulo M, Lopez V, Negron A, et al. Recomendaciones de prevención de infección por coronavirus en las unidades de función pulmonar de los diferentes ámbitos asistenciales. 2020.
31. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by M-mode ultrasonography. *Chest*. 2009;135(2):391–400.
32. NuvoAir AB. EC Certificate Full Quality Assurance System. Stockholm, Sweden; 2017.
33. Hernández CR, Fernández MN, Sanmartín AP, Roibas CM, Domínguez LC, Rial MIB, et al. Validation of the portable Air-Smart Spirometer. *PLoS One*. 2018;13(2):1–11.
34. Minami T, Manzoor K, McCool FD. Assessing Diaphragm Function in Chest Wall and Neuromuscular Diseases. *Clin Chest Med*. 2018;39(2):335–44.
35. Mcnicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*. 2015;2015(6):1–107.
36. Jefatura del Estado. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. Vol. 294, Boletín Oficial del Estado (BOE). 2018.
37. Gerstman B. Basic biostatistics: Statistics for public health practice. 2th ed. Sudbury: Jones and Bartlett; 2015. 274 p.
38. Martinez Gonzalez M, Sanchez-Villegas A, Toledo Atucha E, Faulin J. Bioestadística amigable. 3ª. Barcelona: Elsevier; 2014. 358 p.
39. European Medicines Agency. Guideline for Good Clinical Practice. E6 (R1). 1996. Vol. 1995. 2016.
40. Kang R, Jeong JS, Chin KJ, Yoo JC, Lee JH, Choi SJ, et al. Superior Trunk Block Provides Noninferior Analgesia Compared with Interscalene Brachial Plexus Block in Arthroscopic Shoulder Surgery. *Anesthesiology*. 2019;131(6):1316–26.
41. Kim DH, Lin Y, Beathe JC, Liu J, Oxendine JA, Haskins SC, et al. Superior Trunk Block: A Phrenic-sparing Alternative to the Interscalene Block: A Randomized Controlled Trial. *Anesthesiology*. 2019; (3):1.
42. Hussain N, Costache I, Kumar N, Essandoh M, Weaver T, Wong P, et al. Is Supraclavicular Block as Good as Interscalene Block for Acute Pain Control Following Shoulder Surgery? A Systematic Review and Meta-analysis. *Anesth Analg*. 2020;130(5):1304–19.
43. Schubert AK, Dinges HC, Wulf H, Wiesmann T. Interscalene versus supraclavicular plexus block for the prevention of postoperative pain after shoulder surgery: A systematic review and meta-analysis.

- Eur J Anaesthesiol. 2019;36(6):427–35.
44. Ferré F, Mastantuono J, Martin C, Ferrier A, Marty P, Laumonerie P, et al. Parálisis hemidiafragmática por bloqueo supraclavicular guiado por ultrasonido: un estudio prospectivo , observacional , de cohorte. Brazilian J Anesthesiol. 2019;(xx).
 45. López Escárraga VM, Dubos España K, Castillo Bustos RH, Peidró L, Sastre S, Sala-Blanch X. La ratio de grosor diafragmático (inspiratorio/espíatorio) como método diagnóstico de parálisis diafragmática asociada al bloqueo interescalénico. Rev Esp Anesthesiol Reanim. 2018;65(2):81–9.
 46. Lee JH, Cho SH, Kim SH, Chae WS, Jin HC, Lee JS, et al. Ropivacaine for ultrasound-guided interscalene block: 5 mL provides similar analgesia but less phrenic nerve paralysis than 10 mL. Can J Anesth. 2011;58(11):1001–6.
 47. Renes SH, Van Geffen GJ, Rettig HC, Gielen MJ, Scheffer GJ. Minimum effective volume of local anesthetic for shoulder analgesia by ultrasound-guided block at root C7 with assessment of pulmonary function. Reg Anesth Pain Med. 2010;35(6):529–34.
 48. Albrecht E, Kirkham KR, Taffé P, Endersby RVW, Chan VWS, Tse C, et al. The maximum effective needle-to-nerve distance for ultrasound-guided interscalene block: An exploratory study. Reg Anesth Pain Med. 2014;39(1):56–60.
 49. Hellyer NJ, Andreas NM, Bernstetter AS, Cieslak KR, Donahue GF, Steiner EA, et al. Comparison of Diaphragm Thickness Measurements Among Postures Via Ultrasound Imaging. PM R. 2017;9(1):21–5.
 50. Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. J Appl Physiol. 1997;83(1):291–6.
 51. Kim BG, Han JU, Song JH, Yang C, Lee BW, Baek JS. A comparison of ultrasound-guided interscalene and supraclavicular blocks for post-operative analgesia after shoulder surgery. Acta Anaesthesiol Scand. 2017;61(4):427–35.

Appendix 1

Supplementary data, such as study protocol, IC and DCF of participants, data management details and study data will be uploaded in the study registration of ClinicalTrials.gov Protocol Registration and Results System website, available at <https://clinicaltrials.gov/ct2/show/NCT04385966>.

Figures

Figure 1

CONSORT diagram of REDOLEV-2019 study participant flow (11). Abbreviations: IBPB, Interscalene brachial plexus block; PCA, Patient-Controlled Analgesia; US, Ultrasounds.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITChecklist.REDOLEV2019.doc](#)