

A prospective randomized double-blind trial of the efficacy of a bilateral lumbar erector spinae block on the 24h morphine consumption after posterior lumbar interbody fusion surgery

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Abstract

Background: Spine surgery is associated with considerable postoperative pain and can be challenging to treat. A loco-regional technique suitable for spine surgery should cover the dorsal root of the spinal nerves at the levels where surgery is performed. The erector spinae block is a loco-regional technique with promising results that was recently described at the thoracic level. There are no randomized trials of this technique on a lumbar level. This study tests the hypothesis that the 24-hour postoperative morphine consumption is significantly lower in patients undergoing posterior lumbar inter-body fusion surgery with a lumbar erector spinae (LUMBES) block when compared to a sham block. **Methods:** This prospective randomized double-blind multicentre study will randomly allocate 80 adult patients undergoing elective posterior lumbar inter-body fusion surgery during general anaesthesia to one of two groups as follows: 1. bilateral erector spinae block (20 mL 0.25% levobupivacaine) or 2. bilateral sham block (20 ml NaCl 0.9%). Our primary endpoint is the 24-hour postoperative morphine consumption. Secondary endpoints include: 72-hour morphine consumption, intraoperative sufentanil dosage, postoperative pain scores at regular time intervals both at rest and during movement, time to first post-operative mobilization and the Quality of Recovery 40 score. **Discussion:** The LUMBES trial is a pragmatic clinical study that will provide evidence of whether a bilateral lumbar erector spinae block is effective in reducing 24-hour postoperative morphine consumption in patients undergoing lumbar inter-body fusion surgery. If this hypothesis is confirmed, this finding could contribute to more widespread implementation of this technique.

Background

Background information

Patients undergoing spine surgery often fear postoperative pain, which can be a source of considerable preoperative distress. Many of these patients are already diagnosed as so-called chronic pain patients requiring high doses of narcotics and other analgesics. In spine surgery postoperative pain can often be severe and difficult to treat, certainly if a one-dimensional approach is used to achieve pain control [1, 2]. Many caregivers are reluctant to prescribe liberal doses of opioids to achieve adequate analgesia as this may be associated with side effects such as respiratory depression, sedation and nausea. Many techniques have been combined in order to decrease opioid consumption after spinal surgery e.g. epidural catheters, spinal and epidural morphine or local infiltration[3]. The introduction of ultrasound has allowed the performance of plane blocks and other techniques such as root blocks and facet infiltrations without the use of unreliable 'pop-techniques' or x-ray.

A loco-regional technique suitable for back surgery should cover the innervation of the relevant vertebrae and paravertebral muscles and include the dorsal roots of the spinal nerves at this level[4]. Dorsal ramus blocks have been shown to be feasible in the treatment of chronic back pain [5].

Recently a series of case reports has been described in which bilateral block of the lumbar dorsal ramus nerve resulted in a positive effect on pain scores and morphine consumption after spine surgery [6]. To our knowledge, however, no RCT's have yet been performed to study the effect on pain scores and opioid

consumption. Furthermore, there are promising results for postoperative analgesia with a new plane block, the erector spinae block, which has recently been described as a safe and simple technique for neuropathic and acute postoperative pain at the thoracic level. [7, 8] .

Rationale

Theoretically, an infiltration between the erector spinae muscle and the transverse process provides anesthesia of the dorsal ramus at the same vertebral level. Since the local anaesthetic is injected into a plane, the solution can spread both caudally and cranially via the thoracolumbar fascia, resulting in anaesthesia of the dorsal ramus of the spinal nerves above and below the injected level. The erector spinae block has been described at the thoracic level with promising results. We performed a small feasibility trial in which we found that the erector spinae block could easily be performed without major inconvenience for the patients ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT0321453) NCT0321453). In this proposed trial we aim to determine the effect of a lumbar erector spinae block on pain after back surgery, expressed as morphine consumption during the first 24 hours postoperatively.

Objectives and purpose

In this prospective, randomized, double-blind placebo controlled clinical trial we will investigate the effect of bilateral erector spinae block (20 mL levobupivacaine 0.25%) on the 24-hour postoperative morphine consumption when compared to a sham block (20 ml of NaCl 0.9%) following posterior lumbar inter-body fusion surgery. Secondary objectives include the effect of the erector spinae block (ESB) on the numeric rating scale (NRS) pain scores in rest at fixed time points: at the time of inclusion, in the post anaesthesia care unit (PACU, [T0 = arrival in PACU, T+15min, T+30min]) and on the ward (twice daily- morning and evening until postoperative day 3). Other secondary objectives are the effect of an ESB on the NRS pain scores during defined movement (mobilization to chair) at 24 hours, 48 hours and 72 hours; time to first mobilization to chair (hours); time to first walk of 20 meters (hours); the required sufentanil dose during surgery (micrograms), total morphine consumption during the first 72 hours postoperatively (milligrams) and the Quality of Recovery 40 score (QoR-40) at day 1 and 3.

Methods/design

Study design and registration

This is an investigator-initiated prospective randomized double-blind multicentre trial.

The study is being performed in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and Good Clinical Practice guidelines. The study has been approved by the ethics committee at Antwerp University Hospital, Wilrijk, Belgium and the AZ Klina Hospital, Brasschaat, Belgium (reference: B300201837508) The trial has been prospectively registered at www.clinicaltrials.gov (reference:NCT03825198) and will be monitored by the clinical trial centre of the Antwerp University Hospital.

Participation

Patients scheduled for elective 1 or 2 level posterior lumbar inter-body fusion surgery in the AZ KLINA Hospital and the Antwerp University Hospital will be asked for informed consent by a member of the anaesthesiology department. Recruitment will occur during the preoperative consultation and will open on 15th of February 2019 until the required number of patients have been included.

Inclusion criteria are as follows: (1) American Society of Anaesthesiologist (ASA) physical status of 1-3, (2) Age: 18 - 75 years, (3) normal liver and renal function.

Exclusion criteria are as follows: (1) Body Mass Index (BMI) < 20 or BMI > 35, (2) allergy to one or more medications used in the study including epinephrine, levobupivacaine, dexamethasone, propofol, sufentanil, rocuronium, ketorolac, morphine, ketamine, dehydrobenzperidol, ondansetron, alizapride (3) chronic strong opioid use (>3 administrations per week), (4) contraindications to a regional anaesthetic technique, (4) contraindications to one or more of the study medications, (5) patient refusal and/or no informed consent.

Randomization

Patients will be assigned consecutive numbers upon inclusion in the study. These numbers are 1:1 randomly allocated to the ESB or the sham group using a web-based randomisation system QMinim. Qminim uses stratified randomisation, stratification will be done according to site, gender and levels of surgery. In Qminim a minimisation procedure is used to randomize the patients to ensure a similar distribution of the stratifying arms.

Online randomization will be carried out by an independent anaesthetist who will also prepare the medication.

Medication

The ESB study medication will be 20 ml levobupivacaine 0.25% (Chirocaine, AbbVie). The preparing 20 ml of NaCl 0.9% (B. Braun)

Blinding

All investigators, staff and patients will be blinded to the treatment groups. The study medication will be prepared by an anaesthesiologist who is not involved in the study or in the care of the patient. Both solutions and syringes will appear identical.

Unmasking will only occur after statistical analysis has been completed, unless if medically indicated.

Interventional treatment

All patients will receive a bilateral ESB. The blocks will be performed by experts in the field of ultrasound guided regional anaesthesia. The blocks will be performed preoperatively in a separate block room with ultrasound, after obtaining IV access and application of standard ASA monitoring. The blocks will be placed as described by Chin et al. ⁶ and modified for the lumbar level. The patient will be placed in the

lateral or sitting position. A curved array probe or a high frequency linear probe, depending on the BMI of the patient, will be placed in longitudinal alignment, 2-3 cm lateral to the vertebral column. The transverse processes of the vertebrae at the level of surgery, the erector spinae muscle and the psoas muscle will be identified. In case of two-level surgery, the transverse process of the upper level will be considered as the target. A 5 or 8 cm 22G ultrasound needle will be inserted with an in-plane technique in a cephalad to caudal direction until bone contact with the top of the transverse process is reached. After slight retraction of the needle, 20 mL of the study medication will be injected behind the erector spinae muscle. The same procedure will be repeated on the contralateral side.

General anaesthesia will then be induced in a standardized way with propofol 2-3mg/kg, sufentanil 15µg and rocuronium 0.5mg/kg. After tracheal intubation, anaesthesia will be maintained with sevoflurane and intraoperative analgesia provided with sufentanil. The dosages of these agents will be determined at the discretion of the attending anaesthesiologist. At the end of surgery, patients will receive acetaminophen 1g IV, ketorolac 0.5 mg/kg IV (max. 30 mg) and a morphine loading dose (0.1 mg/kg) IV to manage postoperative pain. Patients will be extubated in the operating theatre and admitted to the PACU. Postoperative nausea and vomiting prophylaxis will be administered with dexamethasone 5mg IV just before induction of general anaesthesia. If required, this will be supplemented by ondansetron 4mg IV and further with alizapride 50mg IV as rescue.

Postoperative pain in the PACU and on the ward will be treated with regular doses of acetaminophen 1g IV around the clock (4 times daily) and by a patient controlled intravenous analgesia (PCIA) pump containing morphine at a concentration of 1 mg/mL and dehydrobenzperidol 0.05mg/ml. The PCIA pump will be programmed as follows: no continuous infusion, a bolus dose of 1.5mg morphine, a lock-out interval of 8 minutes and an hourly limit of 7.5 mg. If pain management on the PACU is inadequate, defined as a Numeric Rating Scale (NRS) pain score > 3 (0 [no pain] – 10 [worst imaginable pain]) additional boluses of 1mg morphine IV will be administered by the PACU nurses with a total additional dose of morphine limited to 0.15 mg/kg. If pain management with morphine remains inadequate, an IV ketamine (Ketalar, Pfizer) bolus (0.2mg/kg) will be administered.

Primary endpoint

The primary endpoint is the morphine consumption during the first 24 hours postoperatively in milligram and will be determined from the PCIA pump.

Secondary endpoints

As secondary endpoint, the total morphine consumption in mg, during the first 72 postoperative hours, will be extracted out of the PCIA pump. Pain scores at rest will be assessed with the NRS (0=no pain, 10 = worst imaginable pain) and tested at regular time intervals: at the time of inclusion, in the post anaesthesia care unit (PACU, [T0 = arrival in PACU, T+15min, T+30min]) and on the ward (twice daily-morning and evening until postoperative day 3). Pain scores during defined movement (first moving to a chair and sitting upright) will be registered. Time to first mobilization to a chair (in hours since T0) and

time to first walk of twenty meters (in hours since T0) will be noted in the patients' study diary. The Quality of Recovery 40 score (QoR-40) will be calculated from the responses to a standard questionnaire at postoperative day 1 and day 3. The QoR-40 is a widely used and extensively validated measure of quality of recovery. It is a 40-item questionnaire on quality of recovery from anesthesia that has been shown to measure health status after surgery[9, 10] .

Tertiary endpoints

Other endpoints include preoperative expected NRS pain score, postoperative nausea and vomiting score according to hospital protocol, number of administered postoperative anti-emetics, time to first meal and time to first defecation. All block complications or adverse events will be registered.

Summary of known and potential risks

The erector spinae block is a plane block where a substantial dose of local anaesthetic is used. As this technique has only recently been described, limited evidence is available regarding the potential risks of the block. The potential risks described below relate to the known risks of a plane block, facet infiltration and intramuscular injection:

Discomfort during puncture

Allergy for the disinfectant or levobupivacaine (very rare 1:10.000- 1:100.000)

Infection at the skin, needle trajectory or point of injection (very rare). The clinical presentation can be variable, e.g. redness at the puncture site or in extreme cases an intramuscular abscess. Therefore, the ESB will be performed under strict sterile conditions using a sterile gown, gloves and mask, and a sterile field.

Bleeding: very rare with the use of an ultrasound-guided technique. When bleeding occurs, this will be noted by the surgeon.

Neural damage: very rare since the target of the puncture is a muscular plane and not the nerve root or nerve ramus itself

Local anaesthetic systemic toxicity: since the doses are substantial there is a clinically significant risk for local anaesthetic systemic toxicity, as with any existing plane block. It can immediately be treated with intralipid. For this reason, the patient will be monitored during and after the placement of the erector spinae block until the start of surgery. Intralipid should be available in any medical environment where regional anaesthesia is performed.

Data collection

Patients' demographic data will be collected at the inclusion assessment (height, weight, age, sex and ASA classification). The attending anaesthesiologist will collect data with regard to the anaesthesia and surgical procedure. Nurses will collect the data in the PACU. When transferred to the orthopaedic ward, the

Acute Pain Service Team will score the Quality of Recovery 40 survey (QoR-40) daily, adjust analgesia when necessary and systematically screen for side effects. Ward nurses will assess NRS pain scores in the morning and the evening on postoperative day 1-3. Morphine PCA consumption will electronically be registered by the PCA pump, all other data will be registered by nurses of the PACU, ward pain department or trial nurses. All medication can be retrieved from the patient data management systems. Complications will be assessed on the day of discharge. During the 72 hours of the trial, data will be registered on paper. After termination of the trial (72 hours after surgery) the data will be directly registered in the software program Open Clinica.

An independent trial monitor from the clinical trial center (CTC) at Antwerp University Hospital will conduct a follow up on the GCP performance of the trial in both study locations. All data will be published anonymously.

Sample size

Our sample size calculation is based on data from a randomised controlled trial comparing the effect of systemic infused lidocaine with placebo, on the 24h morphine requirement in posterior lumbar arthrodesis[11] . We considered a 25% reduction in PCA morphine consumption as clinically relevant. To calculate the sample size, we assumed a mean of 51 mg morphine with standard deviation 19 mg (mean morphine consumption for the placebo group of the above-mentioned trial), a type 1 failure risk of 5% and a type 2 failure risk of 20%. Thirty-five patients are be required in each group to detect a 25% reduction in morphine equivalent over 24 hours. The sample size calculation was based on an independent samples t- test. We plan to include 80 patients in total to compensate for potential dropouts and uncertainty in predicting the actual standard deviation.

Patient characteristics and baseline comparisons

Demographic and other baseline characteristics will be summarized by treatment group. For categorical variables, frequencies and percentages will be reported. Where values are missing, percentages will be calculated for the available cases, and the denominator will be mentioned. Continuous variables will be summarized as mean with standard deviation or median with interquartile range as appropriate.

Comparisons of demographic and baseline characteristics between the treatment groups will be conducted to assess the effectiveness of randomization. For categorical variables the chi-squared test or Fisher exact test (when numbers are low) will be used. For continuous variables, a t-test or Mann-Whitney U test will be used as appropriate.

The following baseline information prior to randomization will be collected: age, sex, BMI, ASA physical status, indication for surgery, preoperative pain (NRS) and use of analgesics.

Analysis of the endpoints

SPSS software version 21 (SPSS, Chicago, IL, USA) or 3.3.2 will be used for statistical analysis. The primary endpoint will be analysed using an independent samples t-test intention-to-treat population (in

case of normality).

To evaluate the sensitivity of the results of the primary outcome analysis, a linear regression will be used to model the cumulative morphine consumption during the first 24h after surgery with treatment as predictor and taking into account possible confounders.

A linear mixed model will be used to model the cumulative morphine consumption over time with subject as random effect. This model allows correction for confounders and adding a random intercept for site. From this model the difference in morphine consumption at the different time points can be estimated.

To compare the continuous outcomes (intraoperative sufentanil dosage, required morphine dose, pain scores, Quality of Recovery 40 score, nausea and vomiting score, number of administered postoperative anti-emetics) at different time points we will use an independent samples t-test if they are normally distributed or a Mann Whitney U test if otherwise. We will also fit a linear regression model for these outcomes, which makes it possible to correct for confounders. A linear mixed model will be studied for the continuous outcomes measured over time.

The time to the different events of interest (first mobilization to a chair, first walk of 20 meters, first meal and first defecation) will be studied in a time-to-event analysis comparing the two treatment arms. If required, we will use a Cox proportional hazard model to adjust for other variables.

Dissemination policy

The trial's results will be submitted to a peer-reviewed journal regardless of the outcome.

Discussion

Posterior spine surgery ranks amongst the most painful surgical procedures and can be challenging to treat. High doses of opioids are often prescribed [1, 2]. Musculoskeletal postoperative pain in posterior approach spine surgery arises from iatrogenic mechanical damage, intraoperative retraction, partial devascularisation and denervation of bone, ligaments, muscles, intervertebral disks and zygapophysial joints. In addition, neuropathic pain arises from compression and damage to nerve roots exiting the spinal canal and sometimes damage to the spinal cord itself[12]. In order to reduce opioid use, loco-regional and local anaesthesia were introduced. In spine surgery loco-regional techniques were limited to epidural catheters, spinal and epidural morphine. These techniques have side effects and are not routinely used. Local anaesthetic wound infiltration is often performed with unfortunately short-lived effect[3]. The loco-regional technique used in this type of surgery should aim to anaesthetise the dorsal root of the spinal nerves at the appropriate operative level[4]. Dorsal ramus blocks have been shown to be feasible in the treatment of chronic pain[5]. Recently, a series of case reports has been described where a bilateral block of the lumbar dorsal ramus nerve showed improved pain scores and reduced morphine consumption after spine surgery[6]. Also, there are promising results with the erector spinae block, which has recently been described as a safe and simple technique for neuropathic and acute

postoperative pain at the thoracic level[8] . Furthermore, ESB has been shown to effectively control postoperative pain in patients undergoing breast surgery. However, no comparative data for the lumbar level is available[13] .

This study will provide clinical evidence on the efficacy of the lumbar erector spinae block in reducing postoperative opioid consumption for posterior lumbar inter-body fusion surgery. If the LUMBES trial demonstrates efficacy, the findings will provide high-quality evidence to support the implementation of this technique in clinical practice. Furthermore, it might trigger studies from other researchers to test our outcomes in their practice.

Potential benefits of the lumbar erector spinae block include the ease of performance with clear landmarks for ultrasound anatomy. The technique is inherently safe, as the target site for injection is a muscular plane and there is practically no risk for mechanical nerve contact. Other benefits include the possible reduction in perioperative opioid consumption. The ESB performed in patients under anticoagulant therapy or with coagulopathies [8] . Furthermore, hemodynamic instability due to sympathetic blockade, as with epidural and spinal anaesthesia, occurs rarely.

Possible risks consist primarily of local anaesthetic systemic toxicity. Since substantial doses are considered necessary, there is a clinically significant risk for Local Anaesthetic Systemic Toxicity (LAST), as with any high-volume fascial block. For this reason, patients need to be monitored according to ASRA (American Society of Regional Anesthesia) guidelines with Intralipid available at all times [14] .

Trial status

Trial status

This document is based on version 8 (02/02/2019) of the original protocol. We anticipate randomizing the first patient on 15th of March 2019 and plan to complete the study in February 2020.

Declarations

Informed consent @ ethic approval

The study is being performed in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and Good Clinical Practice guidelines. The study has been approved by the ethics committee of Antwerp University Hospital, Wilrijk, Belgium and the AZ Klina Hospital, Brasschaat, Belgium (reference: B300201837508)

Informed consent will be obtained from all study participants.

Consent for publication

The document does not contain personal data and consent for publication is not applicable

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and will only be accessible to personnel involved in the trial.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

Margaretha Breebaart, David Van Aken, Olivier de Fre, and Barbara Vervysck drafted the protocol and study design, read and approved the final manuscript

Ella Roelant supported the drafting of the statistical analysis plan.

Luc Sermeus, Lars de Jong, Vera Saldien, Niels Kamerling and Jozef Michielsen read and approved the final manuscript

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Abbreviations

ASA: American Society of Anaesthesiologists

BMI: Body Mass Index

LUMBES: Lumbar erector spinae block

NRS: Numeric Rating Scale

PACU: Post Anaesthesia Care Unit

PCA: Patient Controlled Intravenous Analgesia

QoR-40: Quality of Recovery 40 score

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