Research protocol

Erector spinae plane block for reduction of early postoperative pain scores and opioid use in lumbar spinal fusion surgery, a prospective double-blinded randomized placebo-controlled trial

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Sint Maartenskliniek

Erector spinae plane block for reduction of early postoperative pain scores and opioid use in lumbar spinal fusion surgery, a prospective double-blinded randomized placebo-controlled trial

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACOVA	Analysis of Covariates
AE	Adverse Event
AR	Adverse Reaction
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRF	Case Report Forms
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EMR	Electronic Medical Records
ESPB	Erector Spinae Plane Block
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
LAST	Local Anesthetic Systemic Toxicity
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MAC	Minimum Alveolar Concentration
MEQ	Morphine Equivalents
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
NFU	Dutch Federation of University Medical Centres
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODI	Oswestry Disability Index
PACU	Post-Anesthesia Care Unit
PCIA	Patient Controlled Intravenous Analgesia
PONV	Postoperative Nausea and Vomiting
PROM	Patient Reported Outcome Measure
RASS	Richmond Agitation-Sedation Scale
RCT	Randomized Clinical Trial
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst

Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
VATS	Video Assisted Thoracoscopy Surgery
WKR	Spine Registry
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Lumbar spine surgery is associated with high postoperative pain scores and analgesic use, despite use of multimodal analgesia. The erector spinae plane block (ESPB) is a promising locoregional anesthetic technique for this type of surgery. The literature is not yet conclusive about the effectiveness of this technique on reducing postoperative pain intensity.

Objective: The objective of this study is to evaluate the analgesic effect of ESPB as add-on therapy to multimodal analgesia on early postoperative pain intensity after lumbar spinal fusion surgery compared to placebo.

Study design: The study is designed as a prospective mono-centre, randomized, double-blinded, placebo-controlled trial.

Study population: 76 patients ≥ 18 years of age requiring elective lumbar spinal fusion surgery involving one to four fusion levels.

Intervention: Patients will receive ultrasound-guided ESPB with either ropivacaine or placebo at the end of surgery.

Main study parameters/endpoints: Main study parameter is pain intensity upon emergence from anesthesia measured with the Numeric Rating Scale. A minimal clinically important difference is considered to be a decrease of 1.5 points. Secondary endpoints are acceptability of pain, pain intensity during hospital stay and after 30 days, opioid use during hospital stay and after 30 days, opioid side effects, use of anti-emetics, time to first opioid use/request, length of hospital stay, quality of recovery at discharge

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The Sint Maartenskliniek is experienced in applying locoregional analgesia, the use of ropivacaine and using sonography. The procedure of administering ESPB has a very low risk of complications. Receiving placebo is justifiable because this group will not be withhold standard treatment. The risks of receiving placebo are negligible. The patients will visit the clinic at regular follow-up moments.

1. INTRODUCTION AND RATIONALE

Lumbar spine surgery is associated with high postoperative pain scores and analgesic use.[1] Despite multimodal pain treatment, time to first rescue treatment with opioids is often short and necessary on the Post Anesthesia Care Unit (PACU). Latest scientific insights show most pain interventions produce mild analgesic effects, and advise a multimodal regimen based upon systemic analgesics consisting of at least gabapentoids, ketamine and opioids.[2] Therefore, in our clinic (Sint Maartenskliniek, Nijmegen, the Netherlands), multimodal analgesia in spine surgery is now gold standard, with opioids as first choice postoperative rescue treatment. However, despite multimodal treatment, patients who underwent lumbar spine surgery still develop severe postoperative pain.

A different possible measure to lower the risk of postoperative pain is locoregional anesthesia. The Sint Maartenskliniek has a long history of applying locoregional anesthesia in orthopedic surgery. Locoregional anesthesia provides effective analgesia without systemic side-effects like drowsiness or nausea, thereby reducing perioperative systemic drug use and possibly reducing the risk of persistent postsurgical pain. A novel locoregional anesthetic technique is the erector spinae plane block (ESPB). Good quality evidence exists for the effectiveness of this technique in breast cancer surgery and video assisted thoracoscopy (VATS).[3] Although ESPB seems a promising analgesic technique for lumbar spine surgery patients not responding to the multimodal pain treatment regimen, sufficient high quality evidence is lacking. A recent systematic review summarized the evidence of ESPB for lumbar spine surgery, including two randomized clinical trials (RCT), showing beginning evidence of reduced postoperative opioid consumption and decreased pain scores.[4-6] However, these trials contained a small sample size, were not blinded or lacked a comparator. Furthermore, little information on postoperative hospital stay is provided. This results in ESPB not being widely accepted in lumbar spine surgery. The larger, double-blinded, placebo-controlled methodology in this proposed trial aims to contribute to the scientific evidence for the effectiveness of EPSB in a multimodal analgesia management setting.

2. OBJECTIVES

2.1 Primary objectives and response variable

The primary objective of the study is to evaluate the analgesic effect of ESPB on early postoperative pain after lumbar spinal fusion surgery. Therefore the pain intensity in the postoperative care unit upon emergence, using the Numeric Rating Scale (NRS) for pain, will be the primary outcome parameter of this study.

The null hypothesis states there is no difference in effectiveness of the ESPB compared to placebo on early postoperative pain intensity measured with NRS in patients that underwent lumbar spinal fusion surgery. This hypothesis will be tested two-sided, with $\alpha = 0.05$.

2.2 Secondary objectives

The secondary objectives are to assess the effect of ESPB on:

- Acceptability of pain;
- Opioid use in cumulative morphine equivalent dose (MEQ) in the postoperative care unit and in the first 24 hours after surgery;
- Opioid side effects such as nausea, vomiting and use of anti-emetics in the postoperative care unit and in the first 24 hours after surgery;
- Time to first opioid use/request;
- Length of hospital stay;
- Pain intensity on postoperative admission days, before discharge from hospital, and after 30 days;
- Opioid use 30 days after surgery;
- Quality of recovery on postoperative day 1 and before discharge;
- Complications up to 30 days postoperative.

When postoperative pain is controlled, postoperative recovery is better. Therefore not only postoperative pain scores and opioid use are of interest, but also the quality of recovery after surgery and length of hospital stay. Quality of recovery will be measured using the QoR-15 questionnaire. The QoR-15 provides a valid, reliable, responsive and easy-to-use method of measuring the quality of a patients' postoperative recovery.[7]

3. STUDY DESIGN

This study is designed as a prospective, mono-center, double-blinded, randomized, placebo-controlled trial. The study will be performed at the Sint Maartenskliniek, Nijmegen, the Netherlands. The study will be performed in accordance with the ICH E6(R1) Good Clinical Practice (GCP) guidelines. The duration of the study will be determined according to the progress of inclusion. Patients scheduled for elective lumbar spinal fusion surgery will be studied. Subject of investigation is the locoregional anesthetic technique ESPB. Subjects will be randomized to receive either ESPB with a long-acting local anesthetic or normal saline (placebo).
The staff involved (doctors, nurses, OR-personal), as well as the research team and the patient will be blinded for treatment allocation. The study period includes in-hospital time after surgery and follow-up 30 days after surgery. Placement of the ESPB will be performed according to the study protocol, at the end of surgery, after wound closure. The placement of the ESPB is performed according to daily clinical practice as described by Forero et al.[8] Postoperative treatment of patients will be according to standard hospital protocol for lumbar spinal fusion surgery.

Table 1 displays an overview of the study design and the main procedures that subjects will undergo in the course of research. The trial is registered at http://trialregister.nl/ (NL 9640) and will be monitored.

Table 1: Schedule of enrollment, allocation, interventions/assessments and collection via electronic medical file

Timepoint / Variable	Preoperative	Day of surgery	PACU	POD 1	POD 2	POD 3/discharge	POD 30
Enrollment							
○ Eligibility screening	x						
○ Informed consent	x						
Allocation (ESPB vs. placebo)		x					
Assessment/intervention							
○ Intervention (ESPB or placebo)		x					
○ Surgical procedure/anesthesia		x					
○ NRS for pain	x		x	x	x	x	x
○ Acceptability of pain			x				
○ Opioid side effects			x				
○ Quality of recovery				x		x	
Electronic Medical File							
○ Opioid use	x	x	x				x
○ Use of anti-emetics		x	x	x	x	x	
○ Time to first opioid use			x				
○ Length of hospital stay						x	
○ Adverse events/complications		x	x	x	x	x	x
○ Drain wound leakage			x	x	x	x	Up to 14 days
○ Other study parameters	x						x

ESPB = erector spinae plane block, PACU = post anesthesia care unit, POD = postoperative day

4. STUDY POPULATION

4.1 Population (base)

The study population of this trial will be recruited from the patients planned to undergo elective lumbar spinal fusion surgery with a dorsal surgical approach in the Department of Orthopedics of the Sint Maartenskliniek Nijmegen.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years;
- Patients planned for elective lumbar spinal fusion surgery with a dorsal surgical approach;
- 1-4 level spine fusion surgery;
- Written informed consent.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- A Body Mass Index (BMI) > 40 kg/m^2;
- ASA physical health classification > 3;
- Patients who will undergo spine surgery involving more than 4 levels of fusion, scoliosis surgery*;
- Patients who will undergo minimally invasive surgery;
- Patients who will undergo circumferent spine surgery;
- Patients with an active, local infection or systemic infection;
- Patients with an allergy to one or more medications used in the study;
- Patients with any contraindication to a regional anesthetic technique;
- Kidney- or liver failure inhibiting the systemic use of paracetamol and/or NSAIDs;
- Acute surgeries;
- Patients with a history of drugs or alcohol abuse;
- Pregnancy;
- Cognitive impairment;
- Inability to speak or understand the Dutch language.

* Patients undergoing fusion surgery on more than 4 levels of fusion are excluded because it is unclear whether the ESPB will spread over such wide area. To pursue homogeneity in expected spread of the local anesthetic the inclusion is limited to one to four levels of fusion. Analgesia protocol for scoliosis surgery is different and contains epidural analgesia and is therefore not comparable to the pursued study population.

4.4 Sample size calculation

For sample size calculation an internal database (not published) containing 76 patients who underwent lumbar spinal fusion surgery with dorsal approach containing 1-4 fusion levels

was used. The incidence of NRS ≥ 4 upon emergence in this database was 65%, with a mean NRS score of 4.5 (SD ±2.1).
Level of significance was established to be 0.05. The sample size required having a 80% probability of detecting a difference of at least 1.5 points (NRS 0-10) on the primary outcome early pain intensity between the groups. Breivik et al.[9] described a minimal clinically important difference to be a decrease of 1.5 points on the NRS (scale 0 to 10). Applying the SD of 2.1 from internal data, this translates into an effect size of 0.7. The sample size was calculated using G*Power.

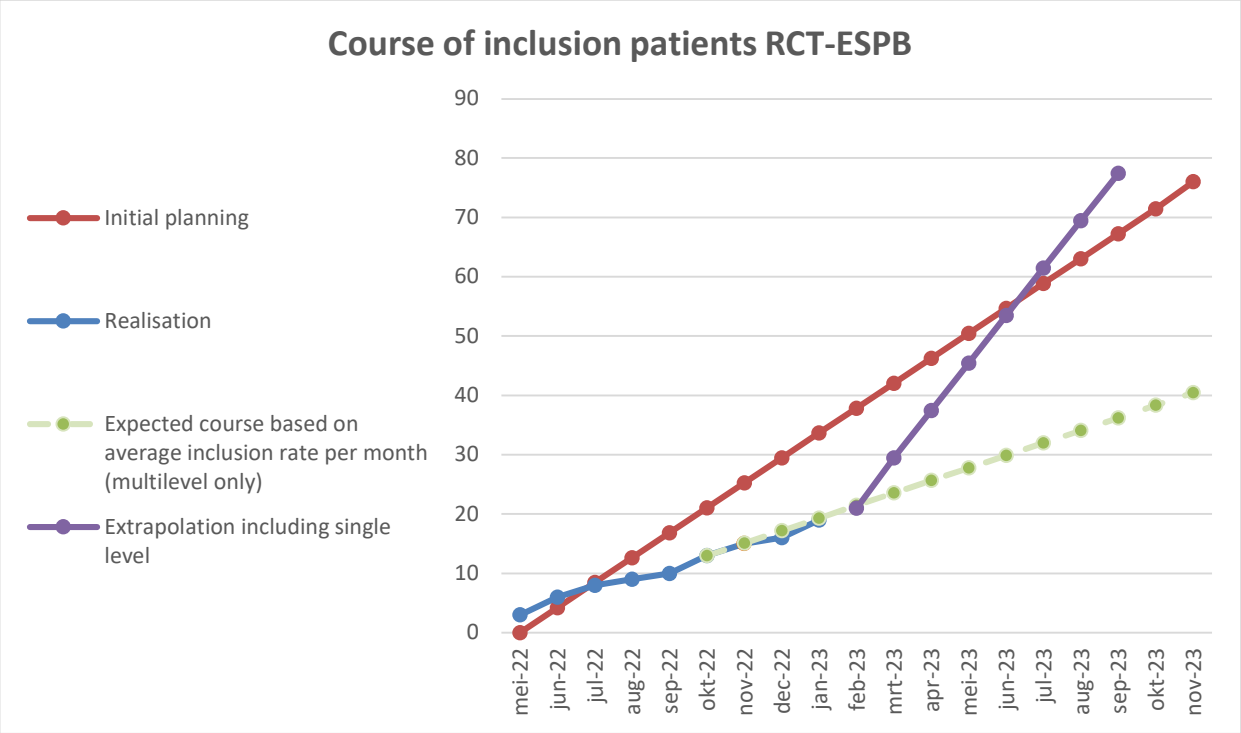
Required sample size to find at least a 1.5 point difference in NRS with an 80% probability and an effect size of 0.7 was calculated to be 68 patients in total. Ten percent withdrawal of the patients (n=7) during the study period is taken into consideration. In order to achieve two equal groups, this is rounded up to a total of 76 patients. The patients will be distributed in a 1:1 ratio.

Mono-centre inclusion
All patients will be recruited in Sint Maartenskliniek as it is a mono-centre study. In 2019 and 2020 approximately 50-60 patients operations meeting our inclusion criteria have been conducted in the Sint Maartenskliniek. Assuming 50-60 patients per year would be eligible for inclusion, with the estimation that 80% of these patients would be included in the study, an inclusion period of 1,5 – 2 years is to be expected.

Addendum 19-01-2023: inclusion rates have been lower than expected (Figure 1). The project team has reviewed the possibility of expanding the inclusion criteria from 2-4 fusion levels to 1-4 fusion levels. Internal data as well as scientific literature show no significant difference in acute pain scores between single- or multilevel surgery.[1] Operation technique is comparable because in both cases open surgical approach is used to carry out the fusion of the vertebrae. Therefore the project team has decided to expand the inclusion criteria.

In 2022, approximately 20 patients per month are operated for single- or multilevel lumbar fusion with a dorsal approach. Assuming 80% of the patients would be eligible for inclusion (no exclusion criteria present) and 50% gives informed consent (based on current inclusion rate), an inclusion period for the remaining 57 patients of ≈ 7 months is estimated (8 patients per month). Figure 1 shows the course of inclusion thus far and extrapolated for the upcoming year. What is shown is the expected/realized inclusion rate for multilevel only (blue and light green), vs. the inclusion rate including single level (purple), compared to the initial inclusion planning (red).

Figure 1: Course of inclusion of patients for the RCT-ESPB



5. TREATMENT OF SUBJECTS

Pre-, peri- and postoperative treatment of patients will be according to a standard protocol for lumbar spinal fusion surgery and is elaborated below. The protocol is also displayed in Table 2.

Preoperative care:

During the study, patients receive standard preoperative care. Basic oral pain treatment will be started preoperatively at the day of the surgery: gabapentine 300 mg, paracetamol 1000 mg and etoricoxib 90 mg. One to two hours before entering the operating room patients receive midazolam 3.75mg orally to relieve stress, if considered contributing by the anesthesiologist and the patient.

General anesthesia, induction:

All surgeries will be performed by nine experienced orthopedic spine surgeons. Intravenous access and routine monitoring will be established in all patients. Induction of anesthesia is according to standard protocol using propofol 1.5-2 mg/kg, sufentanil 15-25 mcg, single dose dexamethasone 8 mg and a single dose of esketamine (10 mg). Endotracheal intubation is facilitated by a single administration of rocuronium (0.3-0.6 mg/kg). Ventilation and hemodynamics are regulated at the discretion of the attending anesthesiologist and/or anesthesia assistant. Patients are placed in prone position after induction.

General anesthesia, maintenance:

Peroperatively, anesthesia via sevoflurane (MAC 0.7-1), esketamine (2.5 mcg/kg/min) and sufentanil (5-25 mcg/h) is continuously administered. Thirty minutes before the end of surgery, esketamine and sufentanil is discontinued and ondansetron 4 mg is administered to prevent postoperative nausea and vomiting (PONV). Thirty to sixty minutes before the end of surgery, a loading dose of morphine (0.1 mg/kg), or in case of contra-indications to morphine, dipidolor (0.2 mg/kg), is given.

The ESPB:

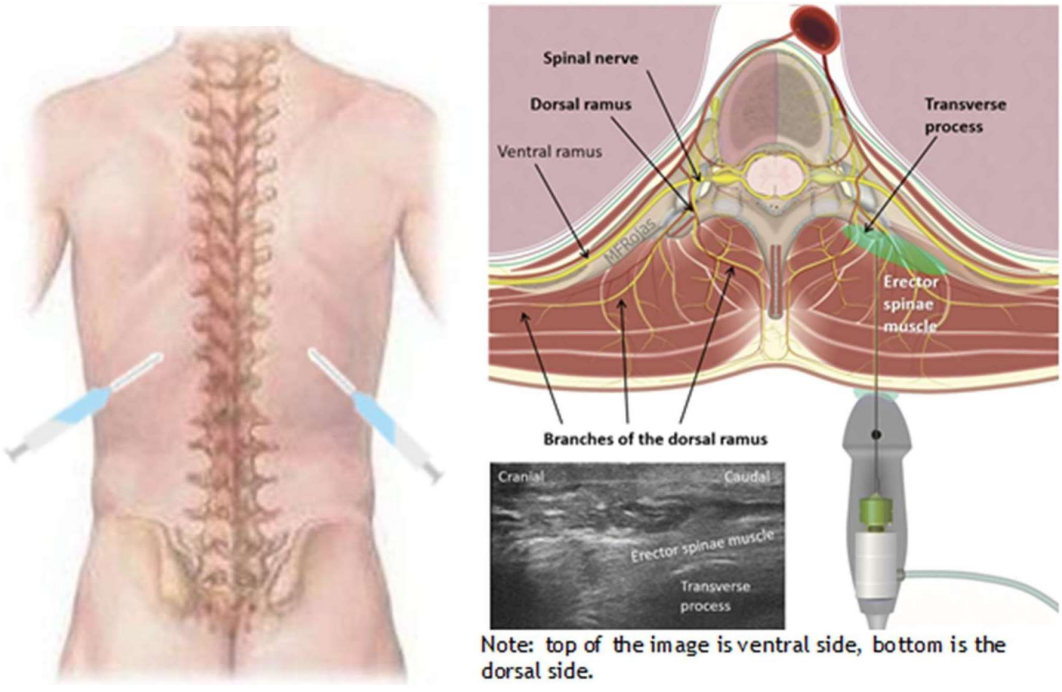
Patients will receive locoregional analgesia via ESPB either with injectate consisting of ropivacaine 0.375 mg/mL with no additives (total dose of 225 mg), which is the intervention group, or injection with NaCl 0.9% (normal saline) with no additives, called the control (or placebo) group. This will occur according to a computer generated randomization list.

At the beginning of the surgery, the orthopedic surgeon marks the transverse processes of the T12 spine level using X-ray and a skin marker, which are used as routine practice to orient before the start of the surgery. The injection will be placed at the end of the surgery in all patients, after wound closure, on both sides of the spine at T12 level (Figure 2). The

patient is still in a prone position (operation positioning), receiving general anesthesia. The placement of the ESPB is performed according to daily clinical practice as described by Forero et al.[8] (Figure 2[10]). The ESPB will be placed ultrasound guided with an in-plane technique. A needle (Tuohy 18Gx5" needle; B Braun, Melsungen, Germany) will be inserted paravertebral at the pre-defined T12 spine level. The needle will be inserted until the transverse process is touched. The needle is then retracted slightly, aspiration will be performed, if no blood returns, 30 mL of the study medication will be injected. The same will be performed on the contralateral side. Patients will receive either a total of 60 mL ropivacaine 0.375 mg/mL (total dose of 225 mg, intervention), or 60 mL NaCl 0.9% (placebo), depending on randomization allocation.

Patients are then placed in supine position and general anesthesia is discontinued. According to normal anesthetic procedure, patients are woken up and extubated. Patients are brought to the Post Anesthesia Care Unit (PACU).

Figure 2: The ESPB is placed bilaterally at T12 level (left). The ultrasound is placed dorsally just lateral from the spine process (right). It shows the transverse process with the erector spinae muscle on top. The injection will be placed in the green marked area and is supposed to anesthetize the dorsal (and ventral) ramus. The injectate spreads caudally and cranially and likewise anesthetizes the dorsal rami at that levels.



Postoperative analgesia regimen:

The postoperative analgesia regimen is according to hospital protocol. Directly post-surgery, on the PACU, specialized PACU nurses can load patients with morphine (or dipidolor in case of contra-indication for morphine) until the patient is comfortable. If respiratory depression occurs, but the patient is still not comfortable, escape medication consists of clonidine intravenously (75-150 mcg) AND/OR recontinuation of esketamin infusion (5-10 mg/hr) AND/OR diazepam (2.5 mg iv or 5 mg p.o.).

The basic postoperative analgesia regimen consists of paracetamol 1000 mg every 6 hours and etoricoxib 90 mg once daily. This is supplemented by a morphine PCIA (patient controlled intravenous analgesia) pump (or dipidolor in case of contra-indication for morphine). The PCIA pump is programmed according to the standard hospital protocol, which is bolus 1 mg, lockout 5 min, max. 32 mg/24h.

Pre- peri- and postoperative treatment of patients will be according to a standard protocol for lumbar spinal fusion surgery and is displayed in Table 2:

Table 2: Anesthesia protocol for lumbar spinal fusion at the Sint Maartenskliniek

Preoperative	**General anesthesia, induction**	**General anesthesia, maintenance**	**Postoperative**
Gabapentin 300 mg	Propofol 1.5-2 mg/kg	Sevofluraan (MAC 0.7-1)	Morphine titrated until comfortable
Paracetamol 1000 mg	Sufentanil 15-25 mcg	Sufentanil (5-25 mcg/h) until 30 minutes before end of surgery	Paracetamol 1000 mg every 6 hours
Etoricoxib 90 mg	Esketamine 10 mg	Esketamine (2.5 mcg/kg/min) until 30 minutes before the end of surgery	Etoricoxib 90 mg once daily
Midazolam 3.75 mg (optional)	Dexamethason 8 mg	Loading dose morfine 0.1 mg/kg (or dipidolor 0.2 mg/kg) 30-60 minutes before end of surgery	Morphine PCIA-pomp (bolus 1 mg, lockout 5 min, max. 32 mg/24h) (or dipidolor)
	Rocuronium 0.3-0.6 mg/kg	Ondansetron 4 mg (30 minutes before end of surgery)	Escape medication: o Clonidine (75-150mcg) o Esketamin (5-10mg/h) o Diazepam (2.5-5mg) o Ondansetron/droperidol

MAC = Minimum alveolar concentration, PCIA = patient-controlled intravenous analgesia

5.1 Investigational product/treatment

Ropivacaine

Our study will evaluate the impact of ropivacaine (0.375 mg/mL) in the application of the ESPB in patients who will undergo lumbar spine surgery. Use of ropivacaine as a locoregional analgesic is widely accepted and therefore not a new study drug. However, the application of this drug is not evidence based for this area of injection.

Mechanism of Action

Ropivacaine causes reversible inhibition of sodium ion influx, thereby blocking impulse conduction in nerve fibers. This action is potentiated by dose-dependent inhibition of potassium channels.[11] Ropivacaine is metabolized extensively in the liver. The kidney is the main excretory organ for ropivacaine, accounting for 86% of the excretion of the drug in urine after a single intravenous dose administration. It has a mean ±SD terminal half-life of 1.8±0.7 h and 4.2±1.0 h after intravenous and epidural administration, respectively.

Bupivacaine is a well-established long-acting regional anesthetic, which like all amide anesthetics has been associated with cardiotoxicity when used in high concentration or when accidentally administered intravascularly. Ropivacaine is a long-acting regional anesthetic that is structurally related to bupivacaine. It is a pure S(-)enantiomer, unlike bupivacaine, which is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.[11] This toxic dose is established to be max 300 mg/dose and 700 mg/24h.

Unlike prior studies, evaluating the effect of ESPB using (levo)bupivacaine in lumbar spine surgery, in this study ropivacaine is used.[5,6,12] The choice for ropivacaine as regional anesthetic in this study is due to this reduced cardiotoxicity and therefore safer drug profile.[11] In the Sint Maartenskliniek ropivacaine 0.375 mg/mL is routinely used as a lower concentration in a higher volume has lower risk of systematic toxicity.

Placebo

The placebo arm of this study will receive 30 mL 0.9% saline bilaterally.

Dose Rationale and Risk/Benefits

The treatment arm of this study will receive single shot injections of 30 mL 0.375% ropivacaine bilaterally on T12 spine level. This encounts for a total dose of 225 mg ropivacaine, which is considered to be a safe dose. The placebo arm of this trial will receive

single shot injections of 30 mL saline 0.9% bilaterally on T12 spine level. Little risk is likely to be associated with this procedure.[13]

5.2 Escape medication

If NRS pain scores exceed three points (scale 0-10) or the patient has unacceptable pain in the postoperative ward, morphine (or dipidolor in case of contra-indication to morphine) can be titrated until the patient is comfortable. If respiratory depression occurs, but the patient is still not comfortable, escape medication consists of clonidine intravenously (75- 150 mcg) AND/OR recontinuation of esketamin infusion (5-10 mg/hr) AND/OR diazepam (2.5 mg iv or 5 mg p.o.).

In case of nausea and/or vomiting, ondansetron or droperidol can be administered. In patients with high risk of PONV ondansetron is preventatively administered during surgery.

This escape medication is part of standard post-anesthesia care protocol. There are no deviations from the standard protocol in terms of choice of medication or dosage.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

- Ropivacaine HCl 7.5 mg/mL solution for infusion (Fresenius Kabi Nederland B.V. Schelle, Belgium)[14]
- NaCl 0.9% solution for injection (B Braun Melsungen AG, Melsungen, Germany)[15]

For product information, we refer to the Summary of Product Characteristics (SPC).

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main study parameter of this study is the early pain intensity in the postoperative care unit after emergence from general anesthesia. Pain scores will be measured using NRS, a scale ranging from 0 to 10 (0 meaning no pain at all; 10 being the worst pain ever experienced). The NRS will be asked by a trained nurse not earlier than one hour after the patient emerges from general anesthesia in the PACU. The patient must have a Richmond Agitation-Sedation Scale (RASS) of 0 to minus 1 in order to determine NRS. If a patient is asleep, no NRS is measured until patient is awake.

7.1.2 Secondary study parameters/endpoints

Secondary endpoints are:

- Acceptability of pain (yes/no);
- Opioid use in cumulative morphine equivalent (MEQ) dose in the postoperative care unit and in the first 24 hours after surgery, extracted from the EMF and PCIA pump (MEQ, dose);
- Presence of opioid side effects: nausea, vomiting and use of anti-emetics in the postoperative care unit and in the first 24 hours after surgery (yes/no);
- Time to first opioid use/request (minutes);
- Length of hospital stay (days);
- Pain intensity on postoperative admission days, before discharge from hospital, and after 30 days (NRS for pain; 0-10);
- Opioid use 30 days after surgery (yes/no, dose);
- Quality of recovery (QoR) using the QoR-15 questionnaire[7] (Dutch version QoR-15NL validation upcoming; 0-150) on postoperative day 1 and before discharge;
- Complications up to 30 days postoperative.

7.1.3 Tertiary study parameters/endpoints

- Drain wound leakage up to 14 days postoperatively.

7.1.4 Other study parameters

- General patient demographics (gender, age, weight, height, ASA classification, comorbidities);
- Baseline biopsychosocial parameters using the STarT Back Screening Tool (Dutch version)[16];
- Surgery indication, type of surgery, duration of surgery (minutes), total amount of blood loss during surgery (millilitres);
- Preoperative use of analgesics (type, dose, route of administration);
- Presence of chronic pain (NRS pain >3 and pain duration ≥ 6 months);
- Preoperative opioid use (yes/no);
- Use of anticoagulants (yes/no).

7.2 Randomisation, blinding and treatment allocation

After obtaining informed consent, the coordinating researcher creates a study case. Patients will be randomly allocated in a 1:1 ratio to either the study group (ESPB) or the control group (placebo) by the hospital's pharmacist on the day of surgery. Permuted block randomization with varying permuted block sizes will be used. This block randomization list will be created by Sealed EnvelopeTM and managed by the hospital's pharmacist. Only the hospital's pharmacist will have access to the randomization list. The staff involved (doctors, nurses, operation room personal), as well as the research team and the patient will be blinded for treatment allocation. The hospital's pharmacist prepares the medication on the morning of surgery, delivers it at the operation complex and collects empty syringes after injection in terms of drug accountability.

7.3 Study procedures

After inclusion and informed consent patients' demographical data will be collected via extraction from our spine registry database. This spine registry is part of the Nijmegen Decision Tool for Chronic Low Back Pain (NDT-CLBP), an internally validated clinical decision tool for low back pain patients, and standard care in the Sint Maartenskliniek.[17,18] The spine registry is implemented in the electronic medical record.

Table 1 displays an overview of moments and procedures of data collection. Data from the electronic medical file (EMF) are collected by the researcher. PACU assessments are conducted by PACU nurses and registered in de EMF: NRS scores, acceptability of pain and presence of opioid side effects in terms of standard care. NRS scores on postoperative days are collected for standard care by the caring nurses on clinical indication. The amount and frequency of opioid usage via PCIA pump will be extracted from the PCIA pump by the researcher. The researcher takes the QoR15

questionnaires from the patient on the first postoperative day and before discharge. Patients will be contacted by the researcher 30 days after surgery to assess pain intensity, opioid use and occurrence of complications.

All surgeries will be performed by one of nine experienced orthopedic spine surgeons. The study intervention (ESPB vs. placebo) will be performed by an experienced anesthesiologist at the end of surgery.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Subjects withdrawn from the study before randomization will be replaced by new included patients. Patients withdrawn after randomization will be lost to follow-up.

7.6 Follow-up of subjects withdrawn from treatment

When patients decide to withdraw from the study, treatment will continue as per hospital protocol. All reasonable efforts should be made to keep in contact with the patient for the duration of the study, to evaluate the clinical condition.

If serious adverse events occur or other adverse events lead to withdrawal, the patient will be treated according to good medical practice and will be closely monitored until recovery.

7.7Premature termination of the study

The trial can be terminated due to the appearance of (serious) adverse events of a nature, severity and duration previously unknown or if known (serious) adverse events occur with an unexpected high frequency. The study coordinator thus has to keep close track of the adverse events.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigator will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the ESPB using ropivacaine, or ESPB with placebo (normal saline). All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded up to 30 days after surgery.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported

within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The investigator will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same investigator and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority (CA).

The expedited reporting will occur not later than 15 days after the investigator has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Method for breaking the code

When a serious AE comes in and if it might be a SUSAR on which additional treatment is necessary, the pharmacist responsible for preparation of the study medication, who is already deblinded, is informed. The attending anesthesiologist, operating orthopedic surgeon, patient and the coordinating researcher are deblinded.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, CAs, and CAs of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 Data Safety Monitoring Board (DSMB)

A data safety monitoring board will not be established.

9. STATISTICAL ANALYSIS

All statistical analysis will be done after consultation with a senior statistician.
Intention to treat analysis will be performed. Continuous data will be described and presented as mean and standard deviation or as median an interquartile range.
Normality of distributions of continuous variables will be assessed with skewness and kurtosis measures.
Missing observations will be reported as missing (not replaced).

9.1 Primary study parameter

The null hypothesis states there is no difference in effectiveness of the ESPB compared to placebo on early postoperative pain intensity measured with NRS in patients that underwent lumbar spine fusion surgery. This hypothesis will be tested two-sided, with α=0.05. A clinically relevant minimal difference in NRS would be 1.5 points.[9] Regression analysis will be used for statistical analysis, with experimental status and pre-operative NRS as independent variables.

9.2 Secondary study parameters

Analysis for 24-hour morphine consumption is conducted as described for the primary study parameter; regression analysis will be used for statistical analysis, with experimental status and pre-operative morphine consumption as independent variables.
Other continuous data (escape medication consumption, length of hospital stay, anti-emetics consumption, time to first opioid use/request, quality of recovery) will be assessed using a Student's t-test if the data are normally distributed. Non-parametric Mann-Whitney U test will be used in case data is not sufficiently normally distributed.
Categorical variables (acceptability of pain and opioid use 30 days after surgery) will be compared between the intervention and control group using the Fisher Exact Test. The mean difference between groups will be presented together with the 95% confidence interval.

9.3 Other study parameters

Baseline data of the two groups (age, weight, height, duration of surgery, blood loss during surgery, as well as gender, ASA classification and type of surgery) will be described.
Preoperative use of analgesics (type, dose, route of administration) will not be analysed but merely described.

9.4 Analysis of covariates

It is hypothesized that there could be a difference in the primary outcome variable (NRS for pain) and the secondary outcome variable (24-hour morphine consumption) between the subgroups defined by factors among which daily preoperative opioid use is most important.[19] Therefore, as secondary analysis the regression for the analysis of the effect of an ESPB on NRS and morphine consumption will be extended with an interaction term between the experimental condition and preoperative opioid use.

To investigate if there is a difference in outcome parameters, an additional analysis will be performed classifying the patients in single- or multilevel fusion surgery. In previous research by Gerbershagen et al., describing pain intensity on the first day after surgery, pain intensity was equal in single and multilevel fusion surgery.[1] As yet, no multilevel ESPB study was conducted.

9.5 Interim analysis

An interim analysis will not be performed in this study.

A safety analysis will be performed yearly, with the formulation of the annual safety report.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted at the Sint Maartenskliniek Nijmegen, according to this protocol, the guidelines in the declaration of Helsinki and later revisions thereof, the ICH guidelines for Good Clinical Practice, in accordance with the Medical Research Involving Human Subjects Act (WMO) and applicable regulatory requirements. No patients will be recruited before written approval has been obtained from the local Medical Ethics Review Committee as well as from the Board of Directors of the Sint Maartenskliniek Nijmegen.

10.2 Recruitment and consent

Patients will be recruited from the list of patients visiting the preoperative screening. The attending anaesthesiologist will screen these patients for eligibility. All candidate-participants will be asked consent for sharing contact data with the investigator. All candidate-participants receive standardized information about the operation. The investigator contacts candidate-participants, will check for eligibility, and, if eligible, the patients will be informed about the study verbally (by telephone by the investigator) and in writing. The terminology in the information sheet is chosen so that the layman can fully understand the content. The patient will be given ample time for consideration and if patients agrees to participate, signed informed consent forms are returned to the researcher (patient receives return envelope).

10.3 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO.

The investigator (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The research data will be managed in accordance with the FAIR principles. Procedures of the Sint Maartenskliniek will be followed for data handling, collection, management, analyses, archiving and reporting. Any calculated data and all digital data will be filed under a study number at the Sint Maartenskliniek Nijmegen, department of Research. The data will be kept for 15 years. A record of the full addresses and names of the study subjects and a copy of the signed informed consent form, which must be able to uniquely identify a study subject, and the corresponding study number will be kept separately. These records are to be retained for 15 years following the completion of the trial.

Baseline patient characteristics and outcome variables will be collected from the spine registry (WKR) database of the Sint Maartenskliniek and enriched with the perioperative anesthetic and surgical procedure characteristics derived from electronic medical records (EMR) as the core set is integrated in the EMR of the Sint Maartenskliniek (HiX). All data entries will be made directly in (electronic) case report forms (eCRFs) using CastorSMS.

Research data will be retrieved from eCRFs, inserted into a SPSS or STATA for statistical analyses and archived in CastorSMS.

Backups of all digital files kept by the Sint Maartenskliniek Nijmegen are updated and stored separately every night. Paper versions of files are stored in an archive in the Sint Maartenskliniek which is only accessible by the Principal Investigator (also doctoral thesis co-supervisor) and the current investigators of the Sint Maartenskliniek.

DANS EASY will be the data repository for open access.

11.2 Monitoring and Quality Assurance

Monitoring and quality assurance will be established according to the advice of the NFU (Dutch Federation of University Medical Centres (NFU)). The classification for risk is estimated at negligible risk. Therefore, the monitoring will consist of the following;

- Frequency of one visit per year;
- Check of rate of inclusion and dropout;
- Check if the investigator file is complete (see ICH E6 (R2) Good Clinical Practice guidelines)[20];

- Check for written informed consent in 1% of participants;
- Check for in- and exclusion criteria of the first 3 participants and 1% of the following participants;
- Verification of source data of 1% of the participants;
- Check for missed SAE's in 1% of the participants and verify reported SAE's;
- Monitoring will be executed by a qualified monitor of the department of Research of the Sint Maartenskliniek Nijmegen, who has successfully attended the BROK-course.

11.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the CA.

Non-substantial amendments will not be notified to the accredited METC and the CA, but will be recorded and filed by the investigator.

11.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC and the CA of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited METC and the CA within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the CA.

11.6 Public disclosure and publication policy

Any publication of the results, either partial or complete, in the form of articles appearing in journals or the verbal presentation by the investigators, or their representatives, requires the agreement of the principal investigator. All participating investigators can use the results of the study for their presentations at conferences, only after contact with the principal investigator (Dr. M. Fenten) and the project leader (drs. I. van de Wijgert). All participating investigators will be acknowledged in the publication(s), and if possible be co-author.

12.STRUCTURED RISK ANALYSIS

12.1 Synthesis

Ropivacaine is used globally and is known as a safe, effective analgesic. A structured risk analysis exists for the application of Ropivacaine HCl and NaCl 0.9% in the Summary of Product Characteristics (SPCs).[14,15] The risks of local anesthetic systemic toxicity (LAST) is extremely uncommon. A prospective clinical registry study performed by Sites et al. (2012) analyzing 12,668 ultra-sound guided nerve blocks showed no cardiac arrests. Other adverse events across all peripheral local anesthetics are postoperative neurologic symptoms, seizure, pneumothorax, unintended venous puncture, unintended arterial puncture and unintended paresthesia during block placement. The total incidence of this adverse events (per 1000 nerve blocks) was 1.8 (95% confidence interval 1.1-2.7).[21]

Bupivacaine is a well-established long-acting regional anesthetic, which like all amide anesthetics has been associated with cardiotoxicity when used in high concentration or when accidentally administered intravascularly. Ropivacaine is a long-acting regional anesthetic that is structurally related to Bupivacaine. It is a pure S(-)enantiomer, unlike Bupivacaine, which is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.[11] This toxic dose is established to be max 300 mg/dose and 700 mg/24h. The choice for ropivacaine as regional anesthetic in this study is due to this reduced potential toxicity and therefore safer drug profile.

Although extensive experience with ropivacaine, few studies on administration of sodium-channel blockers via ESPB exist. No adverse events related to ESPB were found in the 11 included studies with data from 171 patients in a recent systematic review.[4] The procedure of administering ESPB has a very low risk of complications.The structures are easily identifiable via sonography. No critical structures are present nearby the target point.[8,13] The transverse process acts as an anatomical barrier and avoids needle insertion into the pleura or vessels, thus preventing a pneumothorax or hematoma. Moreover, the needle is relatively far from the vertebral canal, which means the risk of spinal cord injury is very low. In a pooled review, which yielded 242 reported cases between 2016 and 2018, only one adverse event (a pneumothorax) was reported.[22] Locoregional anesthesia via an ESPB preserves bladder function and motor neuron function enabling early mobilization. Since motor function is unaltered, immediate postoperative neurological evaluation of spinal cord function is possible.[23]

The Sint Maartenskliniek has a long history of applying locoregional analgesia and our anesthesiologists are very experienced using sonography. This will lower the risk of complications even more.

Receiving placebo is in our opinion justifiable, because this group will not be withhold standard treatment. The administration of ESPB with ropivacaine is an add-on therapy to our standard care. The risks of receiving placebo are negligible.

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