Optimal postoperative Pain management After Lung surgery (OPtriAL): multi-centre randomised trial

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON52222

Source
ToetsingOnline

Brief title
OPtriAL

Condition

- Respiratory tract therapeutic procedures

Synonym
postoperative pain

Research involving
Human

Sponsors and support

Primary sponsor: Maxima Medisch Centrum
Source(s) of monetary or material Support: ZonMw,Maxima Medisch Centrum

Intervention

Keyword: ERATS, postoperative pain, regional anesthesia, VATS

Outcome measures

Primary outcome

The NRS (0-10; 0= no pain, 10=worst imaginable pain) will be used to measure pain scores. The primary outcome measure for *non-inferiority* is the proportion of NRS >=4, defined as the number of NRS >=4 episodes divided by the total amount of NRS pain scores obtained. A minimum of 11 NRS pain scores will be collected (at the recovery room (1), on the ward (10)). The primary outcome for *superiority* is QoR measured with the QoR-15 questionnaire on POD 1 and POD 2. The QoR-15 will provide a continuous variable with a minimum score of 0 and maximum score of 150, and contains the most relevant questions concerning 5 domains (emotional status, physical comfort, psychological support, physical independence and pain) of overall well-being and recovery after surgery.

Secondary outcome

1) Pain scores during rest and mobilisation at baseline, in the morning, afternoon and evening on POD 0-3 and at 2-3 weeks follow-up;

2) Proportion of postoperative pain scores of NRS >=4 during mobilization at POD 0-3;

3) QoR-15 pre-operatively (baseline), POD 0, POD 3 and at 2-3 weeks follow-up;

4) Cumulative use of systemic opioids and analgesics at POD 0-3;

5) Postoperative complications until 2-3 weeks follow-up, according to the Clavien-Dindo classification;

6) Hospitalization, defined as the total number of days in hospital after the

surgical intervention (including readmissions within the first 30 postoperative days). The following standardised discharge criteria after surgery will be applied in all participating hospitals: normal intake of nutrition; independent mobility; absence of fever (<38 °C); and no presence of chest tube.

7) Patient satisfaction (5-point Likert scale: not at all satisfied, slightly satisfied, neutral, very satisfied and extremely satisfied);

8) Degree of mobility (1-4 scale: on the bed (1), to the chair (2), to the toilet (3), outside the patient*s hospital room(4));

9) Cost-effectiveness of analgesic techniques from a health care perspective (see paragraph 10.3.1 *Economic Evaluation*);

10) Patient preferences (study in collaboration with dr van den Akker (health economist, Leiden University Medical Centre) and patient federation *Longkanker NL*, see paragraph 10.3.2 *Patient participation).

Study description

Background summary

Adequate pain control after video-assisted thoracic surgery (VATS) for lung resection is important to improve postoperative mobilisation and recovery, and to prevent postoperative pulmonary complications. Thoracic epidural analgesia (TEA) is the gold standard for postoperative pain management following thoracic surgery. Although the analgesic effect of TEA is clear, failure rates are 9-30% [1, 2, 3] and awake placement is stressful for patients. In addition, TEA is associated with patient immobilisation, bladder dysfunction and hypotension [4]. Based on the best available evidence and the recent guidelines by the Enhanced Recovery After Surgery (ERAS) society, the European Society of Thoracic Surgeons (ESTS) includes early mobilisation after surgery as one of their key recommendations [5].

The disadvantages of the TEA initiated the development of unilateral regional techniques for pain management. Single-shot and continuous paravertebral,

intercostal, serratus anterior and erector spinae blocks have shown to be safe and effective [6]. A meta-analysis on single-shot versus continuous peripheral nerve blockade showed improved pain control, decreased need for opioids and greater patient satisfaction with the continuous infusion technique [7]. Another non-systematic review suggests poorer pain control in single-shot local techniques, however this technique is easy to perform, has low costs compared to the standard TEA care [8] and lower incidence of adverse events [9]. Unilateral regional techniques are not associated with patient immobilisation, bladder dysfunction and hypotension [10].

So far, no consensus exists on optimal postoperative pain management after VATS lung resection. A review of enhanced recovery after thoracic surgery (ERATS) protocols strengthened the lack of unambiguity [11]. The five included protocols all used different techniques for postoperative pain management: oral, intravenous, intercostal, paravertebral and epidural anaesthesia. We conducted a systematic review and found that TEA resulted in mean pain scores of 1.8 (95%-CI 1.4-2.3) at 24 hours after surgery and 1.5 (95%-CI 1.2-1.8) after 48 hours. Regional continuous analgesia resulted in mean pain scores of 2.6 (95%-CI 1.9-3.5) and 2.1 (95%-CI 1.6-2.8) respectively, whereas single-shot regional analgesia resulted in mean pain scores of 2.2 (95%-CI 1.7-2.8) and 1.3 (95%-CI 0.9-1.7). The quality of recovery during the first 2 postoperative days and postoperative analgesia was improved in patients after VATS undergoing single-injection serratus plane block with ropivacaine compared to a placebo control group [12].

The Dutch Societies of Lung Surgery (NVvL) and Thoracic Surgery (NVT) provide no guidelines for postoperative pain management. The Dutch guideline database and the ESTS guideline on ERATS all address TEA as well as other regional techniques to be valid options for pain control after VATS. In January 2018, the NVvL introduced 2 of the 28 knowledge gaps of the Dutch Society of Surgery. The first addresses research on *optimal perioperative management after minimally invasive thoracic surgery*, which should finally lead to a Dutch ERATS protocol. Nationally, an ERATS working group is installed focusing on the disadvantages of TEA: hypotension, the need for a urinary catheter, immobilisation and stressful awake placement of the TEA catheter. There is much interest in the implementation of a multi-modal analgesic regimen without TEA and relying solely on single shot intercostal nerve block and systemic pain control. On the other hand, anaesthesiologists regard TEA as the best current analgesic technique. A survey among Dutch lung and thoracic surgeons indeed pointed out that 69% of hospitals currently use TEA for pain control after VATS lung resection. Of all new regional analgesic techniques, the paravertebral block (PVB) is the only technique with central blockade of both the intercostal and sympathetic nerves. Therefore, next to TEA, PVB fits best in the concept of anaesthesiologists for pain control after VATS lung resection. Internationally, PVB has therefore much attention as regional analgesic technique after VATS. In addition to studying pain, patient satisfaction and postoperative quality of recovery (QoR) are crucial factors in the decision making of patient selected

analgesic techniques. The *Standardised Endpoints in Perioperative Medicine* (StEP) initiative seeks to provide guidance for researchers in their selection of patient-centred outcomes used in clinical effectiveness trials related to anaesthetic-specific interventions [13]. Quality of health is multidimensional and involves QoR as a whole, taking into account physical and mental well-being. Pain assessment continues to be a challenge due to its subjective nature and relation to various outcomes related to QoR, therefore, anaesthesia and pain studies strongly recommend using a patient related outcome measure reporting QoR to assess postoperative pain [14, 15]. To our knowledge, only two articles are published [12, 16] about pain and QoR after VATS using the QoR-40 item questionnaire. Recently, Stark and colleagues [17] developed a QoR-15 item questionnaire, which is proven to be an easy to use short version and is a validated and relevant tool for measuring QoR. The QoR-15 questionnaire contains the most relevant questions regarding physical and mental well-being after surgery and focuses on the following five domains: pain, physical comfort, physical independence, psychological support and emotional state.

Study objective

The main objective is to compare regional continuous paravertebral block (PVB), single shot multi-level intercostal nerve block (ICNB) and thoracic epidural analgesia (TEA) as pain relief techniques in order to provide safe, effective and efficient pain management after thoracoscopic lung surgery. This study will provide the evidence for an ERATS protocol to be implemented for the optimal analgesic technique after VATS anatomic lung resection taking into account pain scores and QoR.

Study design

The proposed multi-centre randomised trial is a three-arm trial comparing PVB, single shot ICNB and TEA in a 1:1:1 ratio for pain (non-inferiority) and for QoR (superiority) in patients who have undergone a thoracoscopic anatomical lung resection. The CONSORT 2010 flow diagram is shown in Figure 1.

Intervention

Intervention 1: continuous regional PVB
The PVB catheter is placed after general anaesthesia at the beginning of the VATS/RATS procedure under direct thoracoscopic vision. If placement cannot be achieved at the beginning of the operation as a result of poor thoracoscopic vision the catheter will be placed at the end of surgery. It is strongly preferred to place the PVB at the beginning of the VATS procedure to benefit from the advantages of administering local anaesthetics from the beginning of the operation. If the PVB is placed at the end of the procedure, patients will need more intravenous opioids during the operation which can interfere with

reliable data collection of pain scores and opioid use in the recovery room.
In order to place the PVB catheter, identify the paravertebral space (an additional option is to use the thorax CT scan for an overview of the landmarks) with the following landmarks: the height of the paravertebral block is at T4-T5 or T5-T6 (carina height), 2-3 cm lateral from the midline and 3-6 cm of depth measured perpendicularly from the skin. After induction of anaesthesia the patient is positioned in lateral decubitus and the relevant landmarks are identified. Optionally, placement of the PVB catheter can be achieved with the aid of ultrasonography. For this, start laterally from the vertebral column and identify the rib and the pleura. Move medially and identify the processus transversus. Locate the middle between two processus transversi and mark the puncture site. Under thoracoscopic vision, identify the sympathetic chain. In all cases the surgeon will identify the paravertebral space under thoracoscopic vision. A Tuohy needle is inserted at the before mentioned marked location and a syringe with NaCl is placed. After feeling a *fascial pop* penetrating the intercostal ligament, feel the loss of resistance when entering the subpleural space. At the same time, observe the appearance of the needle tip under the pleura thoracoscopically. Once the needle is placed in the paravertebral space, create hydrodissection with a minimal amount of NaCl to reach the adequate paravertebral plane for placement of the catheter. Insert the catheter under thoracoscopic vision. Remove the Tuohy needle. Join the connector to the catheter and inject a bolus of local anaesthetic of 15-20 mL ropivacaine 7.5 mg/mL or levobupivacaine 2.5 mg/mL. A ropivacaine 2 mg/mL pump for continuous infusion is given with a infusion rate of 4-10ml/hour, in case of insufficient pain control (NRS >=4) a bolus of 4-5 mL is given (in case a patient controlled (epidural) anaesthesia pump is available with a lockout of 20 minutes). No opioid additives or opioids will be administered through the paravertebral catheter. A provisional stop of the administration of local anaesthetics is planned on the second postoperative day after which removal is considered based on the effect on pain intensity, comparable to the TEA group. No mobility restrictions are needed in this group.

Intervention group 2: single shot ICNB
At the end of the surgery a single shot ICNB will be placed at 6 levels (T3-T8) with bupivacaine 2.5 mg/mL or levobupivacaine 2.5mg/mL and 2-3mL per site under direct thoracoscopic vision. The injection site will be chosen in the intercostal space, just lateral adjacent to the sympathetic trunk. This group will have no analgesic catheters for continued analgesia with local anaesthetics. No mobility restrictions are needed in this group.

Study burden and risks

According to a survey we conducted among lung surgeons and anaesthesiologists in the Netherlands in 2019 asking about the preferred analgesic technique used during VATS anatomic lung resection; 69% performed a TEA, 5.4% used a PVB and 18.2% used an ICNB. The variability, also confirmed through our literature review, indicates no guideline in standard care. Taking into account that TEA

is the most performed technique, benefits in the patients undergoing the intervention techniques will be the omitted epidural related complications (according to our pilot study [18]): 1 day longer immobilisation, 2 days urinary bladder catheter and hypotension (reported to be present in 26% of the patients during POD 1-3).
To the best of our knowledge, the interventions used do not expose participants to additional risks compared to TEA. PVB en ICNB are not experimental and already implemented (inter)nationally. The PVB group has an equal or reduced risk of bleeding, nerve damage, insertion site infection, hypotension, post puncture spinal headache and failure of the analgesic technique compared to TEA. The ICNB group has the lowest risk of complications as it is the most peripheral analgesic technique without the insertion of a catheter. Nonetheless aforementioned risks also apply.
It is realistic to expect that patients in the intervention groups will have more episodes of NRS >=4, therefore, we expect these patients to use more morphine to control pain.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients referred for anatomical lung resection (pneumonectomy, (bi)lobectomy or segmentectomy) with the intention of performing it by VATS or RATS are eligible for the trial. Adult patients older than 18 years who are able to give informed consent and fill out questionnaires in Dutch.

Exclusion criteria

Patients with contra-indications for TEA or PVB (infection at skin site, increased intracranial pressure, non-correctable coagulopathy, sepsis and mechanical spine obstruction) or allergic reactions to local anaesthetics will be excluded. Patients chronically using opioids for reasons not related to the operation will be excluded from the study since postoperative baseline opioid requirement will be higher and TEA remains the preferred technique for these patients. If, prior to the procedure, catheter placement during TEA is unsuccessful, a continuous PVB will be given during the procedure, and, if catheter placement during PVB is unsuccessful, a single shot multilevel ICNB will be used. Non-inferiority will be analysed based on intention-to-treat, as well as per-protocol analysis.
In case the lung surgeon estimates the operation to be performed through a thoracotomy technique instead of a VATS the patient will be excluded.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2021
Enrollment:	420
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-02-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 21054
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-004584-11-NL
CCMO	NL75375.041.20
OMON	NL-OMON21054