Paravertebral vs. Epidural Analgesia for Liver Surgery (PEALS): Protocol for a randomized controlled pilot study [version 1; peer review: awaiting peer review]


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Abstract
Background: Perioperative thoracic epidural analgesia (TEA) is commonly used in hepatectomy patients since it is opioid-sparing and reduces cardiorespiratory complications. However, TEA has a high failure rate and is associated with potentially devastating complications (particularly spinal haematoma) and the risk is likely increased with hepatectomy. Thus, some centres favour systemic opioid-based modalities which, in turn, are associated with inferior analgesia and well-known risks/side-effects. Hence, alternative analgesic methods are desirable. Paravertebral block (PVB) has been used in liver resection with advantages including hemodynamic stability, low failure rates, and low risk of spinal haematoma.
Our purpose is to conduct a blinded, pilot RCT with hepatectomy patients randomised to receive TEA or PVB for perioperative analgesia.
Our hypothesis is that opioid consumption, time to first analgesic request, and pain scores will be comparable between groups, but PVB patients will require fewer perioperative vasopressors/blood products, and have fewer adverse events and a shorter hospital stay.
Methods: With ethics approval, this non-inferiority, pilot RCT with a convenience sample of 50 hepatectomy patients will examine whether PVB imparts analgesia comparable to TEA but with fewer adverse effects.
Primary outcomes are surrogates of analgesia for 72 h postoperatively (i.e., opioid consumption, time to first analgesic request and pain scores at rest and with coughing);
Secondary outcomes are blood products/fluids administered; side effects/complications until 72 h postoperatively; length of hospital stay.

The results will be used to plan a large multicentre trial comparing TEA vs. PVB in hepatectomy patients. This study has a high potential to positively impact the quality/safety of patient care.

ClinicalTrials.gov registration: NCT02909322 (09-21-2016); Available at URL: https://clinicaltrials.gov/ct2/show/NCT0290932

Keywords
Epidural anaesthesia, Non-inferiority trial, Hepatectomy, Paravertebral block, Pilot study, Randomized controlled trial, Regional anaesthesia

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Introduction

Continuous thoracic epidural analgesia (TEA) is commonly used for pain management following hepatectomy\(^1\)\textsuperscript{-5} since it is opioid-sparing, reduces cardiovascular/respiratory complications, and improves mobility.\(^6\) However, the safety of TEA in this population has been debated.\(^7\) TEA is associated with rare complications including epidural haematoma/abscess, and spinal cord injury.\(^8\)\textsuperscript{-10} These risks may be higher following hepatectomy compared to other surgeries because of postoperative coagulopathy and thrombocytopenia.\(^11\)\textsuperscript{-13} Additionally, up to 37% of TEAs fail due to an inadequate block, a dislodged/leaking catheter,\(^1\)\textsuperscript{-10,13}\textsuperscript{-15} or because the catheter has veered to the left (providing analgesia opposite to surgical site). TEA is also associated with hypotension, which may necessitate increased volumes of intravenous (i.v.) fluids perioperatively.\(^11,14,15\) The potential effect of increasing central venous pressure (CVP) with this increased fluid load may exacerbate blood loss and haemodilution.\(^1\) Finally, TEA can delay mobilisation and prolong the need for a urinary catheter. Given these concerns, some centres prefer patient-controlled opioid analgesia (PCA) post-hepatectomy.\(^16\) However, systemic opioids are not as effective for analgesia, and they have serious risk profiles including impaired ventilation, drowsiness, urinary retention, decreased gastrointestinal motility, increased risk of aspiration pneumonia, and postoperative nausea and vomiting (PONV). Thus, there is a continued need for alternative regional analgesic techniques for liver resection patients.

Coagulopathy and/or thrombocytopenia (not uncommon with liver disease),\(^17,18\) worsens in the first two postoperative days following hepatectomy and can remain abnormal for up to five days.\(^4,6,9,19\)\textsuperscript{-22} This is a consequence of preoperative liver dysfunction (reflected by the Model for End-Stage Liver Disease (MELD) score),\(^19\) the amount of tissue resected, blood loss, and intraoperative liver ischaemia.\(^14,23,24\)

Thoracic paravertebral block (PVB) has been used with several surgical procedures,\(^25\)\textsuperscript{-36}\textsuperscript{ including ablation of hepatic tumors and hepatectomy.\(^36\) Previous research suggests that advantages include haemodynamic stability,\(^37,38\) low failure rate,\(^39\)\textsuperscript{-41} and a negligible risk of spinal haematoma.\(^40,41\) However, there is a small risk of pneumothorax.

A right-sided thoracic PVB is a potential alternative to TEA in hepatectomy patients using a right-subcostal incision, but it appears this has not been compared to TEA over an extended time-period. To our knowledge, the only randomised controlled trial (RCT) currently available compared bilateral thoracic PVB to TEA and concluded that TEA provides a modest analgesic benefit.\(^42\) However, patients were only followed for 48 hours which may be insufficient for pain outcomes since hepatectomy patients generally begin to mobilise at 48 hours postoperatively, meaning their pain scores are likely to worsen. Additionally, postoperative coagulopathy and thrombocytopenia generally peak at 48 hours postoperatively and can persist for extended periods depending upon factors including the capacity of the liver to produce α-1-acid-glycoprotein (AAG), albumin, and coagulation factors, as well as its metabolic capacity (mechanisms which protect against local anaesthetic (LA) systemic toxicity (LAST)). This highlights concerns in the above mentioned study,\(^42\) since even patients with normal liver function can develop LAST with a 48-hour infusion of LA via bilateral PVB.\(^42\) In addition, pain from a right subcostal incision probably does not justify using a left-sided PVB which may further expose potentially “LAST-vulnerable” patients to additional LA.

Another study by Richardson \textit{et al.} (1999) found that thoracotomy patients receiving PVB had less pain and improved pulmonary function than with TEA.\(^44\) The TEA cohort also had a higher incidence of PONV, respiratory complications, hypotension, and consumed more morphine.\(^45\) In another study, PVB patients had less PONV, hypotension, and/or urinary retention compared to TEA.\(^45\) A systematic review of RCTs (comprising 1762 thoracotomy patients) concluded that the most effective analgesic method for preserving spirometric function was PVB.\(^46\) A meta-analysis of thoracotomy studies comparing TEA and PVB concluded that PVB is associated with fewer pulmonary complications and less urinary retention, PONV, and hypotension, albeit with comparable analgesia,\(^47\) and this was later confirmed.\(^48\) Based upon such data, we decided to compare a right-sided PVB with TEA for perioperative analgesia following hepatectomy.

Hypothesis

Our hypothesis is that surrogates of pain will be comparable between groups but PVB patients will require fewer vasopressors and i.v. fluids/blood products, have fewer side effects/complications, and have a reduced hospital length of stay (LOS).

Protocol

Sample size

Non-inferiority trials typically require larger samples than superiority trials;\(^49,50\) thus, we anticipate the need to include multiple centres to secure enough participants. Therefore, we propose a single-centre pilot study to generate the data needed to estimate the sample size required for a large, multi-centre trial. Based upon previous studies that compared TEA versus PVB for postoperative analgesia in patients undergoing thoracotomy,\(^51\) we will aim for a convenience sample of
25 patients per group to generate pilot data upon which to base a larger, multi-centre trial. Our non-inferiority margin will be set at 20% for cumulative opioid consumption at 72 hours postoperatively since we do not consider a difference of <20% to be clinically relevant.

Participants, setting and recruitment
A convenience sample of 50 patients scheduled to undergo a hepatectomy through a right subcostal incision will be recruited from our medium-sized (~407 beds), tertiary care academic centre. Eligible patients will be approached by research personnel at the preoperative screening clinic or, because of COVID concerns, via telephone at least 24-48 hours before surgery and given information about the study. For patients who are eligible and willing, research personnel will obtain signed consent while they are waiting to be taken to the operating room (OR). In all cases, both the anaesthesiologist and the attending surgeon will be made aware at least one to three days before surgery of the potential involvement of the patient, and time will be allowed for discussion and withdrawal at their request. With the volume of liver resection surgical patients at our centre (i.e., ~30/year), we anticipate recruitment/data collection for 50 patients to require two to three years.

Eligibility criteria
- Patients will be eligible for inclusion to our study if they are:
  - 18-80 years of age
  - American Society of Anesthesiologists (ASA) physical classification I-III
  - Undergoing elective liver resection through right subcostal incision
  - Proficient in English
  - Competent to provide consent
- Patients will not be eligible for our study if they have:
  - Pregnant or lactating
  - Do not provide informed consent for participation
  - Body mass index <18 or >40 kg.m⁻²
  - Dementia or neurological impairment
  - Jaundice (bilirubin >50 μmol/L)
  - Liver resection combined with a secondary surgical procedure
  - Contraindication to neuraxial block (INR ≥1.6, platelet count <100,000/mm³, fever, previous back surgery)
  - Anticipated significant coagulopathy post-liver resection (as indicated by MELD score >8 or predicted liver resection of >500 g)
  - Contraindications to study medications
  - Any type of extended incision that is not restricted to the standard right subcostal incision
  - Remain intubated in the postoperative period
  - Significant heart disease including moderate or severe valvulopathies, left ventricular ejection fraction <35%, moderate or severe cardiomyopathy of any etiology (e.g., ischaemic, dilated, etc.), previous history of
malignant arrhythmias (ventricular tachycardia/ventricular fibrillation, prolonged QT syndrome, etc.), or any other cardiac conditions deemed as high surgical risk by anaesthesiologist investigators

- Pre-existing chronic pain condition requiring chronic opioid intake for >3 months

**Randomisation**

This is a randomised, controlled, non-inferiority pilot study. Eligible patients will be randomised using a computer-generated randomisation table prepared by the institutional biostatistician with assignments concealed in envelopes. Participants, surgeons, and dedicated research personnel collecting the data (i.e., study nurses/research assistants) will be blinded to allocation. Anaesthesiologists performing TEA/PVB will not be blinded but will have no involvement in patient assessments/data collection.

**Data collection and storage**

To protect confidentiality, patient data on collection sheets/spreadsheets will be identified only by a study identification number that will be linked to the patient identity only on a master sheet/spreadsheet kept securely and separately from the data. Patient data will then be entered into a password-protected REDCAP file and stored on the institutional server behind a firewall. All study data will be retained for the 15-year storage period required by Health Canada following which, it will be permanently deleted and/or destroyed. Only study personnel will have access to identifiable study data and it will not be shared with a third party. Final data may be placed in a public depository but no publicly accessible information will be identifiable.

Descriptive demographic data including patient height, weight, age, sex, ASA physical classification, MELD score, comorbidities, type and length of surgical procedure, number of resected liver segments, estimated blood loss, intraoperative complications, surgeon, the main surgical indication, and preoperative functional liver status will be recorded.

**Study design and ethical approval**

Ethical approval was provided by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (ANAE-270-15) and the study registered on Clinicaltrials.gov (NCT02909322 09-21-2016) available at URL: https://clinicaltrials.gov/ct2/show/NCT02909322. This non-inferiority pilot RCT in which hepectomy patients will be randomly assigned to receive either TEA or PVB for postoperative analgesia, is also in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. As clearly stated in the informed consent, in the unlikely event that participants are injured due to participation in the current study, medical care will be provided to them free of charge until resolution of the problem. By providing consent to participate, they are not waiving their legal rights or releasing the investigator(s) and sponsors from their legal and professional responsibilities.

**Protocol-version 1.4, 03-23-2022**

The standard of care for elective hepatectomy will be followed. Apart from intraoperative management of the regional block and postoperative analgesia, perioperative management will be identical in both groups. After general anaesthesia (GA) induction, invasive monitoring will be with an arterial line with or without a central venous line. Arterial blood gases will be monitored every hour. Fluid management will be at the discretion of the anaesthesiologist. Intraoperative haemodynamics will be managed by adjustment of the depth of GA and vasoactive drugs, and with fluid administration, all at the discretion of the anaesthesiologist. The quantities of crystalloids, colloids and blood products, and the intraoperative fentanyl dosage (up to 5 μg/kg allowed) will be recorded. No long-acting opioid (hydromorphone, morphine) or ketamine will be administered intraoperatively. Prophylactic ondansetron (4 mg) will be administered upon surgical completion. With the exception of unstable patients, tracheal extubation will be carried out in the OR before transfer to the post-anesthetic care unit (PACU). After PACU discharge, patients will be managed in a high dependency unit (step down bed) or the intensive care unit at the discretion of the anaesthesiologist.

**Interventions**

*Control group: TEA*

TEA procedures will follow the standard of care at our centre. The TEA catheter will be sited preoperatively at T7-T9 using the landmark technique, and a lignocaine test dose (4-6 mL of 2% lignocaine with epinephrine 1:200,000) will be given. After GA induction, bupivacaine 0.1% with hydromorphone 10 μg/mL will be infused at 6-10 mL/h and five mL boluses will be allowed at 30 min intervals at the discretion of the anaesthesiologist. Upon admission to the PACU, patient-controlled epidural analgesia (PCEA) will be initiated. The PCEA bolus of the same solution will be set at three
mL with a lockout period of 30 min, and the epidural infusion of the same solution will be set at six mL/h and adjusted in two mL/h increments (or decrements) up to 10 mL/h depending upon pain scores and sensory block tested with ice in the PACU.

If at any time point during the first 72 hours post-surgery patients complain of moderate-severe pain (i.e., >4/10 on a numeric rating scale (NRS) where 0 = no pain, 10 = worst pain imaginable) despite maximal epidural infusion (10 mL/h), a bolus of five mL bupivacaine 0.25% will be given, provided the patient is haemodynamically stable, and the block height will then be re-tested. If two boluses of five mL bupivacaine 0.25% over 60 min (30 min. apart) fail to control pain and there is no demonstrable sensory block upon testing with ice, the catheter will be removed (if coagulation profile allows). The decision to remove the epidural catheter will be made by the clinical management team. Therapeutic failure is defined as catheter removal and/or discontinuation of infusion prior to completion of the study (72 hours postoperative). In this case, patients will be started on a standard i.v. PCA (hydromorphone 0.2 mg/mL, 0.2 mg demand dose, 8 min lockout interval).

**Intervention group: PVB**

PVB will be performed following our standard of care protocol. In the institutional block room, a preoperative paravertebral catheter will be sited on the right side at T7-T9 using the landmark technique or under ultrasound guidance, and a bolus of 20 mL ropivacaine 0.25% will be administered. An infusion of ropivacaine 0.25% at a rate of 0.1 mL/kg/h will be started shortly after induction of GA. In addition, five mL boluses of ropivacaine 0.25% will be allowed at 30 min intervals intraoperatively at the discretion of the anaesthesiologist. Upon transfer to the PACU, patient-controlled paravertebral analgesia (PCPA) will be started. The PCPA bolus will be five mL ropivacaine 0.25% with a lockout period of two hours, and an infusion of ropivacaine 0.25% will be continued at 0.1 mL/kg/h and increased in two mL/h increments up to 10 mL/h, depending on the pain scores and sensory block to ice tested in the PACU. This initial infusion will be continued for the first 24 h after surgery, and then reduced by 25% on postoperative day (POD) two, and further reduced another 25% on POD3 to reduce the risk of LAST.

If at any time point during the first 72 hours post-surgery, patients complain of moderate to severe pain (NRS >4/10) despite maximal PVB infusion (10 mL/h) and if there are no signs of LAST, a bolus of five mL ropivacaine 0.25% will be given, and the sensory block distribution will be re-tested with ice. If two boluses of 5 mL ropivacaine 0.25% over 60 min are unsuccessful in maintaining pain scores <4/10, and there is no demonstrable block on sensory testing with ice, the PVB infusion will be discontinued and the catheter removed (if coagulation profile allows), and the case will be counted as a PVB failure. The decision to remove the PVB catheter will be made by the clinical management team. Therapeutic failure in the PVB group is defined as PVB catheter removal prior to completion of the study at 72 h postoperative. In this case, patients will be started on a standard i.v. PCA (hydromorphone 0.2 mg/mL, 0.2 mg demand dose, eight min lockout interval).

All patients will receive i.v. hydromorphone (0.5-1.0 mg every hour) until they are able to tolerate oral fluids/medications, at which point they will be given oral hydromorphone (1-2 mg every 4 h) as required starting on the morning of POD2. A member of the research team (blinded to randomisation) will assess the presence/severity of pain and PONV. The assessment will be performed 30 min after arrival to the PACU, and at 4, 8, 24, 48, and 72 h postoperatively. We will ask all patients to rate their pain (NRS scale) at rest and with coughing and their PONV at each of the above listed time points. An antiemetic will be offered to any patients with a PONV score ≥ 2 (where 0 = none, 1 = mild, 2 = moderate, 3 = severe (retching/vomiting)). At 72 hours postoperatively, patient satisfaction with analgesia will be assessed.

Notably, our protocol follows the standard institutional practice for TEA and PVB, including specific LAs used and infusion regimens. Any changes to the study protocol will be amended to the approved ethics application and communicated to all involved in study execution.

**Adverse events**

Serious adverse events (SAEs) such as epidural haematoma or abscess, pneumothorax, LAST, serious respiratory depression, massive transfusion, refractory hypotension, myocardial infarction, will be reported as per standard of care for our centre and also to the institutional research ethics board as required. All SAEs will be documented and discussed by investigators. If deemed to have potentially resulted from the study protocol, the study will be halted pending further independent investigation.

**Outcomes**

The primary outcomes will be pain surrogates during the first 72 hours postoperatively: cumulative opioid consumption, time between the end of surgery and first analgesic request, pain scores (NRS) at rest and with coughing 30 min following arrival to the PACU and then at 4, 8, 24, 48 and 72 hours postoperatively (Figure 1).
Secondary outcomes will be PONV scores, patient satisfaction with analgesia (where 1 = very poor, 2 = poor, 3 = satisfactory, 4 = good, 5 = excellent) at 72 hours, and success/failure of TEA/PVB (Figure 1). Haemodynamic parameters will also be recorded (i.e., mean arterial pressure (MAP), CVP (if applicable), urine output, acid-base data, total volume i.v. fluids (crystalloids, colloids, and blood products) and vasopressors given perioperatively up to 72 hours postoperatively), the number of days to resume a full oral diet, hospital LOS, and any complications/side effects. Additionally, postoperative adverse events will be recorded, including hypotension (MAP<50 mmHg) requiring intervention, respiratory depression, sedation (Ramsay score), urinary retention, and pruritus.

Statistical analyses
Data will be entered into REDCAP and then imported to SPSS (ver. 28.0 for Windows, Armonk, NY, 2020) for data analysis. Data will be analysed using an intent-to-treat strategy, regardless of whether the catheter is removed early. Since intent-to-treat strategies are often “anti-conservative” when used in non-inferiority trials,52 we will also analyse our data using the per-protocol strategy, excluding those participants who were excluded, lost, or deviated from the protocol. All

![Figure 1. Schedule of enrolment, interventions, and assessments.](Link to figure)
Discussion
After major surgery such as hepatectomy and other upper abdominal surgery, inadequate analgesia can lead to hypertension, tachycardia, pulmonary splinting, and inability to breathe deeply and cough. The result could be myocardial ischaemia, pneumonia, and/or the need for prolonged respiratory support. Over-reliance on opioids can lead to excessive sedation, poor pulmonary toilet, constipation, delayed mobilisation, and can lead to long-term opioid dependence. Use of regional analgesia can mitigate the risks associated with systemic opioids. Although TEA does provide satisfactory postoperative analgesia and remains our current standard of care for liver resection patients, it still has a significant failure rate, and disadvantages (outlined above) with respect to haemodynamic instability, pruritus, urinary retention and lower limb weakness. It is also associated with other rare but potentially devastating complications (i.e., haematoma, abscess and/or spinal cord injury). A right thoracic PVB has a much lower risk of spinal cord injury, and less (or even a negligible) chance of causing hypotension, lower rates of limb weakness, pruritus, urinary retention, and a zero chance of ‘veering to the left’. However, it does carry small risks of pneumothorax and LAST. Because PVB is used less frequently than epidurals, some anaesthesiologists may find a PVB technically more challenging.

Study status: Currently recruiting.

Dissemination plans
This study will be used to design a powered, multi-centre RCT comparing TEA to PVB in hepatectomy patients. This work has a high potential to positively impact the quality and safety of care in the liver resection patient population with a reduction in associated costs. Upon completion, study results will be disseminated through international conferences and peer reviewed publication(s). Results will also be communicated to anaesthesiologists and hepatic surgeons at other centres.

Data availability
No data are associated with this article.

Reporting guidelines
Queen’s University Dataverse. SPIRIT checklist. DOI: https://doi.org/10.5683/SP3/M0VO8N53

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All authors reviewed and approved the final manuscript for submission and can attest to the originality of this work. In addition, all authors made important intellectual contributions.

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