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Overview

Epidurals for liver transplantation – Where are we?

MILAN ZOKA[1]
VIMI REWARI[2]

[1]Consultant Anaesthetist, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK

[2]Associate Professor, Department of Anaesthesiology and Intensive Care, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

Correspondence:
Zoka Milan
Department of Anaesthesia
Lincoln Wing, St James's University Hospital
Beckett Street, Leeds LS9 7TF, UK
E-mail: z.milan@leeds.ac.uk

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Abstract

Thoracic epidural analgesia (TEA) has been used as a mode of postoperative pain relief for orthotopic liver transplants (OLT) in a selected group of patients. It is not widely practiced in view of the impaired haemostasis associated with end-stage liver disease and severe unpredictable intraoperative coagulopathy. TEA in OLT may not be the technique of choice for routine administration of postoperative analgesia, but can be considered in patients who have a normal coagulation profile preoperatively. Safe conduct of TEA in OLT involves anaesthetic expertise and stringent monitoring in the postoperative period. This review discusses the status of thoracic epidural analgesia in patients undergoing an orthotopic liver transplant.

INTRODUCTION

Orthotopic liver transplantation (OLT) is now an established treatment for end-stage liver disease. A successful outcome is largely dependent on a multidisciplinary approach in the perioperative management of a liver transplant (LT) recipient. The anaesthetist forms a very important part of this team and contributes significantly not only to intraoperative management, but to postoperative care as well. Provision of postoperative analgesia forms an important part of postoperative care for an LT recipient.

Thoracic epidural analgesia (TEA) provides the most efficient peri- and postoperative analgesia following major abdominal surgery, which includes liver resection and living donor hepatectomy *(1–4)*. It also decreases postoperative morbidity and mortality (5). However, its use is not popular in patients with end-stage liver disease *(6, 7)*. This is mainly due to concerns regarding an epidural haematoma due to a grossly deranged coagulation profile in this patient population and rapid changes in intra- and postoperative coagulation related to frequently unpredictable liver dysfunction. Thoracic epidurals as a mode of postoperative analgesia in LT recipients are not only challenging but controversial as well. In this review, we attempt to discuss the current status of epidural anaesthesia and analgesia in LT surgery.

Intensity of pain in LT recipients

Considering that an LT is the biggest of major abdominal operations in terms of duration, stress for the patient and the surgical team involved, and the size of the surgical subcostal incision, it is logical to expect that the postoperative pain is the most intense of all major abdominal operations.

Indeed, the surgery is performed via a large, bilateral subcostal incision extending from the cephalad to the xiphoid process, commonly referred to as the 'Mercedes-Benz incision'. A bilateral subcostal incision

means that breathing and coughing will augment the already intense postoperative pain in this group of patients *(6)*. Furthermore, surgical equipment that keeps the already large incision wide open for a long intraoperative period further contributes to intense intra- and postoperative pain.

However, nociceptive pain is most intense during the dissection phase, during which the enlarged liver has to be often separated from the surrounding structures. Once the native liver is removed, nociceptive pain decreases because the donor liver has no nerve connections with the recipient. The new liver is usually smaller than the native liver, and the pain caused by abdominal distension from ascitic fluid and an enlarged native liver in an LT recipient becomes less intense following donor liver implantation.

In addition, metabolism of all pain relief medication is affected by the pre-reperfusion, non-functioning liver. Following reperfusion of the donor liver, metabolism of analgesics improves significantly if the donor liver is working well.

There is a common sentiment among anaesthetists that OLT recipients need less analgesia than patients who undergo other major abdominal surgery. This viewpoint has not been confirmed in the literature. Only 1 study has reported that OLT patients experience less pain and require a lower dose of morphine postoperatively than liver resection patients do *(8)*. From our clinical experience, we know that LT patients can suffer from severe pain because of the large surgical incision in the upper abdominal region, and they may require large amounts of opiates in the postoperative period.

Epidural Analgesia – Why should it be used?

The aim of an effective analgesic regime is to provide patient comfort by preventing postoperative pain, but at the same time avoiding the adverse effects of analgesic agents. Epidural analgesia fulfils most of the above criteria, and is therefore the gold standard of postoperative analgesia. TEA is the most common mode of analgesia in major abdominal surgery. As TEA reduces systemic narcotic requirements, it is associated with less postoperative sedation, better postoperative bowel function, better preservation of pulmonary function through easier pulmonary toilet, and earlier ambulation *(9, 10)*. Meta-analysis of randomised controlled trials on the influence of different anaesthetic and postoperative analgesic regimens on pulmonary outcome found that thoracic epidural anaesthesia and analgesia using opioids and local anaesthetics was associated with a decreased incidence of atelectasis, pulmonary infections, and hypoxaemia as compared with systemic opioids *(11)*. On the other hand, another study evaluating subgroup analyses to identify specific types of patients who may have benefited from epidural analgesia in a large trial *(9)* found no difference in the outcome between epidural and control groups in subgroups at increased risk of respiratory or cardiac complications. No differences were found in the length of stay in intensive care or in the hospital. The authors found no evidence that perioperative epidural analgesia significantly influences major morbidity or mortality following major abdominal surgery *(12)*.

As none of these trials included LT recipients, it is safe to assume that even though TEA provides optimal pain management in upper abdominal and thoracic surgery, its effect on postoperative complications and outcome benefits as compared to intravenous analgesia in LT surgery needs further evaluation.

Despite severe postoperative pain and the advantages of TEA described above, most centres practice the use of intravenous patient-controlled analgesia (IV-PCA) for postoperative pain control in LT recipients *(6)*. In the subsequent text, we will discuss controversies related to epidural analgesia in LT patients.

TEA in OLT – The Controversies

Patients awaiting liver transplantation frequently have a deranged coagulation profile associated with end-stage liver disease. The coagulopathy is a result of impaired synthesis of clotting factors, thrombocytopenia, and platelet dysfunction *(13)*. Prolonged international normalized ratio (INR), prothrombin time (PT), partial tromboplastin time (aPTT), and thrombocytopenia are common findings on the day of surgery in LT recipients. Massive surgical bleeding can further deteriorate coagulopathy. A prolonged anhepatic phase can lead to fibrinolysis. Coagulopathy can follow an unpredictable course in the post-reperfusion phase *(14)*. Use of a bypass with heparin-coated bypass lines and/or release of heparin-like substances from the donor liver can contribute to further deterioration of clotting.

Postoperatively, coagulation factor levels and platelet count increase steadily toward normal values in the presence of a normally functioning graft *(15)*. With such deranged blood clotting, an epidural haematoma, a catastrophic complication of epidural catheterisation, is the worst fear of every LT anaesthetist. A study from Sweden suggests that the frequency of hematoma is 1.3–2.7 per 100,000 neuraxial anaesthetics *(16)*. The risk is probably increased in patients with impaired haemostasis due to coagulopathy, which is frequently present in LT recipients, or therapeutic anticoagulation, also present in LT recipients, as antithrombotic drugs are used to prevent hepatic artery thrombosis and deep venous thrombosis *(17)*. There is also a concern for local anaesthetic toxicity as the amides in local anaesthetics are metabolised in the liver. In a recent study, patients who received TEA for liver resection revealed significantly higher levobupivacaine concentrations as compared to patients undergoing anterior rectal resection *(18)*. This should be kept in mind with patients whose graft does not function optimally in the postoperative period.

TEA in OLT – The evidence so far

Although we are aware that TEA has been used for postoperative analgesia in a small proportion of LT recipients, there is very limited evidence in the literature regarding the use of TEA in OLT. By searching the literature, we found only 1 retrospective study published recently, several case reports, 1 abstract presented at a Liver Intensive Care Group of Europe (LiCAGE) meeting, and an extensive exchange of opinions on the topic on the LiCAGE website.

Case reports are related to the paediatric LT population, where fast tracking was recently introduced with great benefit to LT recipients *(19)*. Diaz *et al*. described the first successful use of thoracic epidural anaesthesia as an adjunct for peri- and postoperative analgesia in paediatric liver transplantation *(20)*. An epidural catheter was inserted at the T8-T9 level after induction of anaesthesia. The authors injected the anaesthetic solution, which consisted of 10 mL of 0.2% ropivacaine with 45 μg of clonidine and 300 μg of morphine, before removing the catheter. The child could be extubated on the table and did not require any analgesic drug during the first 24 h *(20)*. Kim and Harbbot reported the use of caudal epidural anaesthesia in a paediatric liver transplant. They used single-shot morphine without a local anaesthetic due to concerns for intraoperative hypotension. The child could be extubated on the table and remained pain free for the next 6 h *(21)*.

In 2010, Trezebicki and colleagues published the single largest study on the use of TEA in OLT *(22)*. The authors described their 10-year experience in the use of TEA in 67 patients undergoing OLT. TEA was performed by experienced anaesthetists in patients with INR < 1.5, APTT < 45 s, platelets > 70 G/L, and a normal thromboelastogram *(22)*. The authors assessed extubation time, frequency of complications, and undesired accidents. From 279 patients undergoing LT, TEA was performed on 67 (24%), and from these, 56 (84%) were extubated in the operating theatre. There were 5 cases of unsatisfactory analgesia and 1 case of accidental removal of the epidural catheter. Serious complications of TEA were not reported from any of the patients. The authors concluded that TEA is a safe component of anaesthesia in a selected group of patients undergoing OLT that allows early extubation *(22)*. The limitation of the study is that it was not a randomised controlled trial and did not compare the outcome benefits of TEA with that of IV opioids.

The abstract presented at a LiCAGE meeting in 2003 presented a review of the practice at King's College Hospital, where TEA has been used for LT recipients since 1990 *(23)*. They had 1654 LT recipients (1232 adults and 422 children) between 1990 and 2000. The overall rate of TEA use was 9.7%; usage was higher in adults (11%) than in the paediatric population (5.5%). The commonest cause of liver disease in patients receiving TEA was primary biliary cirrhosis, followed by primary sclerosing cholangitis and amyloidosis. Interestingly, the highest preoperative INR in patients receiving epidural analgesia was 4.0, and the lowest platelet count was 32 G/L. They reported minor complications, namely backache and inadequate analgesia. The retrospective study, performed 10 years ago in the biggest transplant centre in the UK, failed to demonstrate the benefits of TEA in LT recipients in terms of early extubation *(23)*.

TEA in OLT – Our practice

At our centre, TEA has been used on LT adult recipients for the last 20 years in a carefully selected group of patients. Our approach, including that towards TEA, has changed over the last 2 decades in many ways. Our current practice regarding TEA is as follows: patients likely to be candidates for TEA receive an oral explanation about TEA, including possible complications, during anaesthetic preassessment. They also receive a booklet about anaesthesia for LT that includes an explanation of TEA. When we are certain that they understand the procedure, they sign a written consent form for LT and anaesthesia, which includes TEA. We use TEA in the selected group of patients with normal preoperative clotting and that we plan to fast track. We ensure that the patients have an INR of <1.5, APTT of < 45 s, and a platelet count of >80.000. An experienced anaesthetist inserts an epidural catheter at the T8–T9 level in a patient who is awake or asleep. We use remifentanil for intraoperative analgesia. The epidural catheter is activated at the end of surgery when a carefully titrated bolus of 10–20 mL of 0.125% bupivacaine with 2 μg/mL of fentanyl is administered.

Postoperatively, analgesia is continued with an epidural infusion of 0.125% bupivacaine with 2 μg/mL of fentanyl at 5–15 mL/h. Pain scores, sensory level, and haemodynamic parameters determine the rate of the epidural infusion, which is gradually decreased on daily basis. Paracetamol is prescribed as background anaesthesia; tramadol is prescribed as a rescue analgesic. If the analgesia is inadequate, epidural analgesia is discontinued and the patient is administered PCA-IV morphine.

The epidural catheter is usually removed on postoperative days 3–4, when pain is less intense, and after ensuring a normal coagulation profile. Tramadol or morphine PCA-IV is used following epidural catheter removal, depending on pain intensity *(24)*.

In conclusion, TEA in OLT may not be the technique of choice for administration of postoperative analgesia, but can be considered in patients who have a normal coagulation profile preoperatively (*e.g.* patients with primary biliary cirrhosis and primary sclerosing cholangitis). The benefits provided by the TEA should be weighed against the risks of an epidural haematoma.

The safe conduct of TEA in OLT requires anaesthetic expertise and stringent monitoring in the postoperative period. Coagulation parameters should be monitored regularly until after catheter removal. The epidural catheter should be removed only if the coagulation profile is normal. Alternatively, any residual coagulopathy should

be corrected with blood products before catheter removal. Frequent neurologic testing should also be carried out while the epidural catheter is in place and for 12 h after its removal.

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