Role and safety of epidural analgesia

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Introduction

Treatment of pain after upper abdominal surgery is important for several reasons. Not only is it to ensure patient comfort, but also how it contributes to facilitate ambulation and prevent pulmonary complications. Thoracic epidural analgesia (TEA) is probably the most widespread technique for pain relief in thoracotomy and major upper abdominal surgery. It provides excellent pain relief, and the quality of analgesia may be sufficient to justify its use, regardless if outcome is improved or not.

Wheatley reviews most aspects of postoperative epidural analgesia in general. Two recent Cochrane-reviews compare epidural with intravenous analgesia. Continuous epidural analgesia proved superior to patient controlled opioid analgesia in relieving postoperative pain for up to 72 hours after abdominal surgery, but was associated with higher incidence of pruritus. The other review states that administration of epidural local anaesthetics to patients undergoing laparotomy reduces gastrointestinal paralysis compared with systemic or epidural opioids. This was with comparable postoperative pain relief, and no significant differences in PONV were observed. Carli could demonstrate that the superior quality of pain relief provided by epidural analgesia in colorectal surgery had a positive impact on mobilisation and bowel function with long-lasting effects. In the accompanying editorial Wu discusses how this can affect the health-related quality of life.

In the last few years, several original reports, meta-analyses and reviews on the effects of neuraxial blocks on outcome have been published. Even if the overall postoperative mortality, the incidence of myocardial infarction and pulmonary morbidity showed some reduction, however inconsistent, the power to assess subgroup effects was limited. The validity of these analyses has been questioned on the basis of design and protocol of the included studies. Among the major concerns with protocol design the following were noted: Did patients have thoracic epidural catheters placed according to the site of surgery? Were local anaesthetics given throughout surgery? Was inhalational and intravenous anaesthesia standardised in relation to epidural dosing? Exactly how was postoperative analgesia provided and how was breakthrough pain documented and treated? What other components of multi-modal pain treatment did patients receive? The author’s conclusion was, not to throw away Touhy needles and epidural catheters.

Concerning the advantages of these blocks there are some data showing that high-risk patients receive benefit from the combined use of general and epidural anaesthesia in abdominal surgery, but this practice has not been extensively studied in liver surgery. The reason for published data on TEA in liver surgery being so sparse, is probably concerns with pre- and postoperative coagulation, and its effect on epidural catheterisation risk. In one study there was a biliary group but data specifically dealing with liver surgery could be found in the study by Wu only. In this study a database of almost 69,000 mixed surgical patients was analysed, with regard to the effect of postoperative epidural analgesia on morbidity and mortality. The overall use of epidural was 19% and in the hepatectomy group it was 24%. Mortality at 7 and 30 days after surgery was significantly lower in the group where epidural analgesia was used. The total number of patients that underwent liver surgery was low (170) and no conclusions were presented for this sub-group.
In the review by Redai and the papers by Matot and Siniscalchi, more information can be found on aspects of anaesthesia in liver surgery in general, and on epidural analgesia in particular. In this presentation however, I have chosen to focus on areas of controversy in most recent years.

**Pre- vs postoperative**

The question whether there is a pre-emptive effect or not has been addressed in several studies recently, some of them with bearing on thoracic- and upper abdominal surgery. Yegin studied 61 patients that underwent thoracotomy with epidural analgesia started preoperatively in only one group, but with patient controlled analgesia given postoperatively in both. They found that the preop-TEA group scored significantly better than the postop-TEA group when pain after surgery was compared. Cywinski compared pain control in right lobe donor hepatectomy patients with a retrospectively studied group of patients that underwent major hepatic tumour resections. Thoracic PCEA was used in both groups but not started until after surgical incision. Pain scores were higher in the donors, but the study design, mixing different types of patients (preoperative pain, psychology), duration of surgery, data acquisition and lack of rescue treatment protocol, makes the problem with this kind of research obvious. In a meta-analysis published this year, several interventions of the multi-modal concept were compared with regards to their pre-emptive effects. Epidural analgesia scored equal to local wound infiltration and NSAID administration on analgesic consumption and time to rescue request but postoperative pain intensity was less. Taura studied the effect of epidural morphine plus ketamine in 104 cirrhotic patients (Child A) undergoing hepatic surgery. In these patients morphine metabolism and postoperative encephalopathy is a real concern. Quality and duration of analgesia was significantly better in the group that received both epidural ketamine and morphine. Unfortunately intravenous ketamine was given at induction and the epidural drugs were administered postoperatively.

**Awake vs asleep**

Is performing thoracic epidural anaesthesia in an anesthetised adult patient outright malpractice or compassionate care and acceptably safe practice? Published data are insufficient, or refer to retrospective non-controlled studies and can therefore not be used to support either view. There is also great variation in this practice within Europe where caution is advised in most countries. In addition to many case-reports, at least one study with an accompanying editorial on this matter has been published in the last couple of years. The number of reported patients is impressive (4298 in total) and included abdominal, thoracic and combined operations. It is noted however, that this study is restricted to epidurals inserted at a lumbar level and mainly used for postoperative pain relief. In the study there were no neurological complications or radicular symptoms noted. However, the authors point out that with a confidence interval of 95% the estimated risk of having serious neurological injury from neuraxial blocks could be as high as 0.08%. To what extent this risk will increase when performed under general anaesthesia has not been quantified. It is concluded that more substantial justification is needed as one moves cephalad along the neuraxis, where the severity of injury is likely to increase. One further finding in this study was the absence of clinically evident spinal haematomas, even though the majority of the patients underwent thoracotomy and received standard heparin thromboprophylaxis. Tsui reports that direct cord injury can occur without paraesthesia, whereas pain is more common in lesions affecting the nerve roots. The risk of permanent paraplegia and delayed detection is discussed in a case report and an editorial.

**Risks & Coagulation**

The risks of neurological complications of neuraxial blocks have been summarised in recent reviews. The incidence of persistent neurological deficit was reported 0.005-0.07%. In another survey of 450 000 epidural blocks (including 200 000 in obstetric patients) the incidence was 0.006%.

In the Consensus Conference Statement, published in the May 2003 issue of Regional Anesthesia and Pain Medicine (2003;28:172-97), it is stated that “numerous studies have documented the safety of neuraxial anesthesia and analgesia in the anticoagulated patient. Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration……. New challenges in the management of the anticoagulated patient undergoing neuraxial blockade have arisen as medical standards for the prevention of perioperative venous thromboembolism were established. Likewise, as more efficacious anticoagulants and anti-platelet agents have been introduced, patient management has become more complex……..It is important to note that although the consensus statements are based on a thorough evaluation of the available information, in some cases, data are sparse. Variances from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist.”
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Time from DA to ED</th>
<th>Time from ED to DA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extrinsic pathway XII, XI, X</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>3-5 days, INR &lt; 1.5*</td>
<td>&lt; 24 h before</td>
<td>*safe for surgery (R)</td>
</tr>
<tr>
<td><strong>Intrinsic pathway II, VII, IX, X</strong></td>
<td></td>
<td></td>
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<tr>
<td>Heparin low-dose s.c. (aPTT &lt; 1.5 x norm.)</td>
<td>4 h*</td>
<td>1 h</td>
<td>*ASRA 2 h</td>
</tr>
<tr>
<td>Heparin full-dose i.v.</td>
<td>12 h*</td>
<td>2 h*</td>
<td>*Controversial</td>
</tr>
<tr>
<td>LMWH once-daily</td>
<td>10-12 h</td>
<td>(6-8 h postop.) 2 h*</td>
<td>*24 h if blood during ED</td>
</tr>
<tr>
<td>LMWH twice-daily or higher dose</td>
<td>24 h</td>
<td>(24 h postop.) 2 h</td>
<td></td>
</tr>
<tr>
<td><strong>Common pathway AfIII, IIa, Xa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>see above</td>
<td>see above</td>
<td></td>
</tr>
<tr>
<td>LMWH Dalteparin, Enoxaparin, Tinzaparin …</td>
<td>see above</td>
<td>see above</td>
<td></td>
</tr>
<tr>
<td>Pentasaccharide Xa-inhib. Fondaparinux</td>
<td>avoid</td>
<td>8-12 h*</td>
<td>*Controversial</td>
</tr>
<tr>
<td><strong>Platelet antagonists (COX-inhibitors)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>3 days*</td>
<td></td>
<td>*ASRA no restriction.</td>
</tr>
<tr>
<td>NSAID</td>
<td>1-2 days*</td>
<td></td>
<td>*ASRA no restriction.</td>
</tr>
<tr>
<td><strong>Platelet antagonists (Thienopyridines)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Clopidorel (Plavix) potent effect on bleed.time</td>
<td>7 days</td>
<td></td>
<td></td>
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<tr>
<td>Ticlopidine (Ticlid)</td>
<td>14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet antagonists (Glycoprot. PG IIb/IIIa)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>2 days</td>
<td></td>
<td></td>
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<tr>
<td>Eptifibade, Tiroliban</td>
<td>8 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thrombin inhibitors (Hirudin derivatives)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no statement*</td>
<td>no statement*</td>
<td></td>
<td>*Insuff. data</td>
</tr>
<tr>
<td><strong>Thrombolytics (Streptokinase, t-PA)</strong></td>
<td>no statement*</td>
<td>no statement*</td>
<td>*Insuff. data</td>
</tr>
</tbody>
</table>

So where does this leave us? The pragmatic approach of many anaesthetists is probably to accept an increase in PT (INR < 1.5) and aPTT of up to 50% above normal and a platelet count in the region of > 80.000 (>50-100.000). Likewise would we use a neuraxial technique 4 hours after low-dose heparin or 12 hours after low molecular weight heparin (LMWH) thromboprophylaxis. Accordingly we wouldn’t give heparin until 1 hour or LMWH until 2 hours after placement or removal of an epidural catheter.

The safety of this practice is supported by the reports by Canto and Pastor from the same institution. In a total of 1019 patients a thoracic epidural was inserted prior to CABG or valve replacement surgery where cardiopulmonary bypass with systemic heparinisation was used. Anti-platelet medication was stopped one week before surgery and they used the following inclusion criteria; APT < 45 seconds, INR < 1.5 and platelet count > 80.000/µL. No neurological deficits were detected in either study.

Donor heptatectomies offer a unique opportunity to observe the effects of major resections on tests of coagulation, without the confounding influences of underlying liver disease as reported in several articles.38-40 They describe changes in coagulation tests after heptatectomies (increases in PT and APT) with concomitant decreases in platelet counts. Predisposing factors for postoperative coagulopathy is the amount and quality of the residual liver parenchyma and whether it has been exposed to ischemia, by total or selective vascular occlusion, or not. The main effects on coagulation are encountered on the first to third postoperative day, with peak changes in PT on postoperative day 2 and platelets on day 3. It was assumed that the changes in coagulation correlated with liver function, but the importance of intraoperative blood loss and dilution coagulopathy needs to be accounted for separately.
In a study by Tsui, patients undergoing partial hepatectomy were at an increased risk over other patients for delayed epidural catheter removal. The reasons were either persistent pain or transient coagulopathy. 53 thoracotomies and 142 upper abdominal operations were included in this study of 413. The mean epidural duration was 6.2 days (range 5-9) for the patients with delayed catheter removal. No neurological complications were recorded, but the authors recommended that one should continue frequent neurological assessments in most if not all patients for 24 hours following epidural catheter removal.

To some extent the occurrence of postoperative liver failure and coagulopathy can be predicted. Scoring systems exist that are based upon clinical and laboratory data, but also on function diagnostics and CT-volumetric measurements. According to these publications critical functional remnant liver volume in extended hepatectomy is 25 % (or 250 ml/m²) and > 40 % in presence of preoperative liver dysfunction. An indocyanine green ICG(15 min) retention rate of 15 % is claimed to be a cut-off point for when major hepatectomy is safe. There is also a pulse spectrophotometric application of this technology.

The risk of meningitis or epidural abscess is in the range of 0.004-0.05 %. Important observations in the latter study was that patients with epidural abscess had a longer mean catheterisation time, that perioperative anticoagulant therapy was involved in most cases and that the majority of the patients were immuno-compromised. One can speculate that all patients undergoing major hepatic resections have a potential for becoming immuno-deficient. With an extended resection the patient looses a considerable part of the reticulo-endothelial system and its Kupffer cells, thus making the filter, that should prevent intestinal bacteria from entering the systemic circulation, insufficient. Maybe this is one of the many explanations why sepsis and blood-borne infections are more common in patients with liver failure.

Physiology

An intraoperative regimen, with intermittent vascular inflow occlusion in combination with low central venous pressure, has been shown to lower median blood loss and postoperative morbidity and thereby improve outcome. The technique of total hepatic vascular occlusion imposes greater haemodynamic responses and fluid shifts with potentially detrimental effects on the cardiovascular system and liver function. Another means of reducing the backflow pressure to the liver, apart from low CVP, is by avoiding positive pressure ventilation postoperatively. Much has been written on early extubation in cardio-thoracic surgery, but it is my belief that fast tracking is as important in liver surgery.

The changes in vascular tone resulting from the use of thoracic epidural anaesthesia are well known, but the importance of fluid loading is increasingly questioned. The sympathetic block normally extends at least two dermatomes above the sensory level. This block causes venous and arterial vasodilatation with a drop in vascular resistance of about 15-20 %. The decrease in cardiac output is under normovolaemic conditions usually < 10 % unless the block reaches T4 or above. In such a high neuraxial block, heart rate decreases as a result of blockade of the cardio-accelerating sympathetic nerves. It was demonstrated that epidural anaesthesia per se does not lead to any change in intravascular volume. Even if the same haemodynamic response can be reached with both fluids and vasopressors, the latter approach may be preferred in the treatment of hypotension due to epidural anaesthesia. Most of us acknowledge the importance of avoiding fluid overload in patients with cardiopulmonary diseases, but this is probably equally important in liver surgery!

Technical aspects

Nowadays it is a well established that catheter-insertion congruent analgesia is important for earlier return of gastrointestinal function, reduces the incidence of cardiovascular complications, and provides superior quality of analgesia. For procedures such as oesophagectomy, gastrectomy, hepatic resection and Whipple’s operation, this means that the catheter should be inserted at the T6-T9 level with 3 (-5) cm advanced into the epidural space. The paramedian route is the preferred approach. Testing is recommended, and a dose of 3 ml 2% lidocaine plus 1:200000 epinephrine is often used. For continuous infusion a mixture of bupivacaine 1-1.5 mg/ml plus fentanyl 1-2 µg/ml is common practice. There is little debate on the choice of local anaesthetic, but ropivacaine and levobupivacaine are increasingly used today.

When it comes to the use of neuraxial opioids the pictures is more complex. The risk of developing complications (respiratory depression, nausea, pruritus and urinary retention) makes some clinicians reluctant to use this additive. The lipophilic opioids (fentanyl, sufentanil) have a more rapid onset, shorter duration and
minimal CSF spread (hence relatively greater systemic effect and less respiratory depression expected) as compared with the hydrophilic morphine. The incidence of nausea, vomiting and pruritus is lower. Likewise, it is claimed that the effects of bolus injections are spinally mediated as opposed to the systemic or supraspinal effects of epidural continuous infusions. Ginosar finds support for this claim when analysing this apparent conflict in the literature. The two tables below contain data, extracted from the literature regarding pharmacokinetic properties and dose recommendations, which may be useful.

Thoracic epidural analgesia regimens / opioid use – Compiled data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid Solubility</th>
<th>Mid-Thoracic Bolus Onset (min)</th>
<th>Duration (hr)</th>
<th>Continuous Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>~1</td>
<td>1-5 mg</td>
<td>40-60</td>
<td>12-24</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>~800</td>
<td>50-100 µg</td>
<td>10</td>
<td>2-4</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>~1800</td>
<td>10-30 µg</td>
<td>5</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Thoracic epidural analgesia regimens / LA + opioid combination – Compiled data

<table>
<thead>
<tr>
<th>Analgesic Solution</th>
<th>Continuous rate (mL/hr)</th>
<th>Demand dose (mL)</th>
<th>Lockout interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0625-0.15 % bupivacaine + 2-5 µg/mL fentanyl</td>
<td>4-6</td>
<td>2-4</td>
<td>10-15</td>
</tr>
<tr>
<td>0.0625-0.15 % bupivacaine + 0.5-1 µg/mL sufentanil</td>
<td>3-5</td>
<td>2-3</td>
<td>10-15</td>
</tr>
<tr>
<td>0.1-0.2% ropivacaine + 2-5 µg/mL fentanyl</td>
<td>3-6</td>
<td>2-5</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Several adjuvants to neuraxial blocks have been studied. Adrenaline initiates, via its α1-agonistic effect, vasoconstriction which slows down systemic absorption and increases neuronal uptake. Often 5-20 µg/h is infused. Ketamine is an NMDA-antagonist (N-methyl-D-aspartate) that when administered in a dose of 1-2 mg/h inhibits excitatory transmission and possibly prevents wind-up. The α2-agonist Clonidine (10-20 µg/h) produces analgesia by activating the descending noradrenergic inhibitory system. Both Ketamine and Clonidine appear to have some pre-emptive effects according to recent reports. Adenosine and the GABA-agonists (γ-aminobutyric acid) Midazolam and Gabapentin are all drugs that are currently researched for their future potential of producing analgesia and preventing postoperative hyperalgesia.

As an alternative method to the thoracic epidural in patients with manifest or expected coagulopathy, Karmakar has described the thoracic paravertebral block and his group studied its use in a small series of patients undergoing liver resection. It is a promising technique but its effectiveness needs to be tested in larger studies.

Personal views on thoracic epidurals in liver surgery

# Activate the epidural intraoperatively and preferably prior to incision, regardless if you believe in a pre-emptive effect or not.
# Insert the catheter at an appropriate level (T6-T9) to achieve congruent analgesia.
# Use the epidural as long as needed, which normally is 3-5 days.
# Minimise haemodynamic consequences – avoid large doses of concentrated local anaesthetics. Use test dose and bolus opioid followed by a continuous infusion of the post-op mixture.
# Don’t let the use of epidural anaesthesia lead to excessive fluid loading – judicious use of low CVP and vasopressors intraoperatively is probably best.
# Practice fast track extubation – an option more likely to be successful with a well working thoracic epidural.
# Expect postoperative problems with coagulation when calculated residual liver mass (i.e. functioning parenchyma) is less than 250 mL/m² (25 %) or ICG(15 min) retention > 15 %.
# Use function testing (Thrombelastography) for decision making when coagulation is borderline.
References


16. de Leon-Casasola OA. When it comes to outcome, we need to define what a perioperative epidural technique is. Anesth Analg 2003;96:315-8.


