Comparison of three different epidural solutions in off-pump cardiac surgery: pilot study

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Background. Immediate extubation using thoracic epidural analgesia (TEA) has become more popular after off-pump coronary artery bypass grafting (OPCAB). In this randomized prospective double-blind study, we present the first comparison of preoperative and postoperative hemodynamics during different regimens of TEA for immediate extubation after cardiac surgery.

Methods. Sixty patients undergoing OPCAB were enrolled in this study. TEA was installed >1 h before application of heparin at levels T2–T4. Analgesia was provided by bupivacaine 0.25%, 8 ml, 15 min before surgery and extubation, and at 10 ml h⁻¹ during surgery and up to 72 h afterwards using one of the following regimens: bupivacaine 0.125% alone, bupivacaine 0.125% with fentanyl 3 µg ml⁻¹ or bupivacaine 0.125% with clonidine 0.6 µg ml⁻¹. Patients were block-randomized for one of the three treatments. Pain scores and infusion rates of TEA were assessed up to 48 h after surgery. Respiratory function was assessed by PaO₂ and PaO₂ immediately after surgery, and haemodynamic stability was recorded in the form of heart rate and diastolic and systolic blood pressure.

Results. Patient characteristics, respiratory function and haemodynamic stability did not vary between the three groups. Pain control was very good and was not significantly different between the groups using similar infusion rates after surgery. Paraesthesia in dermatomes T1 or C8 occurred equally in all three groups. There was no neurological complication related to TEA in this study.

Conclusions. We conclude that immediate extubation after OPCAB using TEA is feasible with different TEA regimens. Respiratory function, haemodynamic stability and pain control are not different between TEA with bupivacaine alone, bupivacaine with fentanyl or bupivacaine with clonidine.


Keywords: anaesthesia, general; analgesia, epidural; haemodynamics, side-effects; pain control, outcome; surgery, off-pump coronary artery bypass grafting

Accepted for publication: August 12, 2005

Epidural analgesia has been shown to be advantageous in different types of surgery.¹ It has gained in popularity in cardiac surgery over the last decade. Thoracic epidural analgesia (TEA) provides good protection from stress response,²,³ ensures haemodynamic stability,⁴ allows early extubation,⁵ improves distribution of coronary blood flow and reduces demand for oxygen.⁶ Patients have better postoperative pulmonary function and less postoperative pain.⁷,⁸ It has also been suggested that TEA reduces the incidence of respiratory complications such as pneumonia, and perioperative arrhythmias such as supraventricular tachycardia.⁹,¹⁰ A variety of epidural solutions have been used in cardiac surgery including ropivacaine alone,¹¹,¹² bupivacaine alone⁵,¹³ and bupivacaine with either opioids⁶ or clonidine.⁹,¹⁴ To the best of our knowledge, there is no study comparing the effects of these different epidural solutions in cardiac surgery. In this prospective pilot study, we studied the impact of three epidural solutions on intra- and postoperative haemodynamics as the primary outcome. Postoperative pain scores, complications and side-effects of TEA were evaluated as secondary parameters.
Methods

The study was designed to be prospective, randomized, double-blinded and controlled. Institutional and review boards approved the investigation, and written informed consent was obtained from all the patients. Sixty patients undergoing off-pump coronary artery bypass grafting (OPCAB) (left mammarian artery, where possible, and saphenous vein grafts) were included and randomized to receive one of three epidural solutions: bupivacaine 0.125% alone (group B, n=20); bupivacaine 0.125% and clonidine 0.6 μg ml⁻¹ (group BC, n=20); bupivacaine 0.125% and fentanyl 3 μg ml⁻¹ (group BF, n=20). Before surgery, patients were familiarized with and consented to the thoracic epidural and ultra-fast-track protocol (immediate extubation in the operating room).

Patients having beating heart surgery aged between 18 and 85 years and with an ejection fraction ≥30% were included. Exclusion criteria were refusal to participate, pregnancy, patients with a contraindication for the insertion of an epidural catheter (e.g. abnormal coagulation parameters) and patients refusing the insertion of an epidural catheter.

Routine monitoring included five-lead ECG, invasive blood pressure using a femoral artery catheter, central venous pressure using subclavian venous access, pulse oximetry, BIS monitoring (Aspect 2000 Monitoring System, Aspect Medical Company, MN, USA) and transoesophageal echocardiography (TOE).

Anaesthesia was performed in the same fashion for all patients. On arrival in the operating theatre, an epidural catheter was inserted at T2–T4 under local anaesthesia. The catheter was inserted using a midline approach in all patients with less than three attempts for insertion. Exclusion of spinal or intravascular placement was performed using lidocaine 1.5% with epinephrine 5 μg ml⁻¹. The epidural catheter was discontinued 48–72 h after surgery.

Anaesthesia was provided by fentanyl 3 μg kg⁻¹ followed by propofol 1–2 mg kg⁻¹, and endotracheal intubation was facilitated by rocuronium 0.6 mg kg⁻¹. Intermittent positive pressure ventilation was performed to maintain an end-tidal carbon dioxide between 4 and 4.7 kPa. Intraoperative anaesthesia was maintained by sevoflurane titrated to maintain a BIS of 40–50, and analgesia was provided by epidural analgesia according to group assignment in a double-blinded way. Ringer’s lactate 6–10 ml kg⁻¹ h⁻¹ was given.

In all groups, a bolus (4–8 ml) of bupivacaine 0.25% was given 15 min before skin incision and 15 min before extubation in the operating theatre. The epidural rate was started at 10 ml h⁻¹ after the bolus and kept stable during surgery.

Active temperature control was achieved with forced air warming therapy (BAIR Hugger blankets for the lower body and head, Augustine Medical Company, Eden Prairie, MN, USA) and increased room temperature (≥22°C). During the ischaemic period, treatable bradycardia was defined as a heart rate <40 beats min⁻¹ and was treated with increment doses of ephedrine 5 mg i.v. Hypotension was defined as a systolic blood pressure <70 mm Hg and was treated with increments of phenylephrine 50 μg i.v. Heparin 150 IU kg⁻¹ was given 5 min before ischaemia for all patients (and antagonized using protamine 1 mg for each 1 IU of heparin after completion of the bypass grafting) and at least 1 h after epidural catheter placement.

Extubation criteria were as follows: a cooperative and alert patient; complete neuromuscular function assessed by train-of-four (TOF) >0.8 at the adductor pollicis muscle; oxygen saturation >96% on FiO₂=100%; end-tidal carbon dioxide <6 kPa; stable haemodynamics; core (bladder) temperature ≥35°C. Temporary pacing, an intra-aortic balloon pump or inotropic medications were not considered as contraindication to extubation.

After extubation in the operating theatre, patients were transferred to the post-anaesthesia care unit (PACU) for a short-term stay. After a stay of 2 h in the PACU, patients were transferred to the intensive care unit (ICU) if haemodynamics and respiratory conditions were stable and analgesia was adequate. In the ICU, patients received twice daily heparin 5000 IU. s.c. for thromboprophylaxis for 3 days after surgery. The epidural rate was kept at 10 ml h⁻¹, and then adjusted to between 6 and 14 ml h⁻¹ depending on the pain experienced by the patient. Before surgery, the patients were familiarized with a numerical rate score to assess their pain (0=no pain to 10=maximal imaginable pain). If patients had a pain score ≥4 on the numerical pain scale of 0–10 in the thoracic area, the epidural rate was increased in increments of 1 ml h⁻¹ every 2 h and a bolus of 3–5 ml was given. The rate was decreased if there was paraesthesia in dermatome C8 or higher in a painless patient. Doses of morphine 5 mg s.c. were available for pain in areas not covered by the epidural catheter, such as leg wound pain.

We recorded patient characteristics, preoperative medical status, current medications and left ventricular function as well as operative data (number of grafts, time of ischaemia, haemodynamics), any complications and time to extubation.

Pain scores were recorded immediately after surgery and at 6, 24 h and 48 h after surgery. Postoperative blood pressure and heart rate were documented for the first 6 h after surgery. Complications such as bleeding, haemodynamic problems, arrhythmias and respiratory dysfunction were also noted. The state of awakening was continuously evaluated during the first 24 h after extubation (evaluated as awake, sleepy but responsive to verbal command or non-responsive) and then routinely on the surgical ward. Nausea, pruritus and episodes of paraesthesia were recorded during the whole stay in the hospital. Neurological symptoms, such as muscle weakness in the legs or arm were noted and led to discontinuation of TEA, followed by neurological investigations.

All data were compared using repeated measures analysis of variance (ANOVA) within groups and multiple comparison
ANOVA between groups for continuous data. The data of proportions were compared using the χ²-test. A P-value <0.05 was considered significant. The group size was calculated to find a 20% difference of mean diastolic or systolic blood pressure 4 h after surgery with a power of 0.8. This difference was defined as being of clinical significance before the study.

**Results**

There were no significant differences in age, sex, weight, ejection fraction, number of grafts and ischaemic time between the three groups (Table 1). The incidences of past myocardial infarction, stroke, hypertension, diabetes, chronic obstructive pulmonary disease or renal insufficiency were also similar. Room and body temperature at the beginning of the surgery and at the moment of extubation were no different between the three groups.

The insertion of the thoracic epidural catheter was successful in all patients. The catheter was taken out at the end of the surgery and none required re-intubation. The mean (SD) of time (min) without any group-related difference.

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine 0.125% (n=20)</th>
<th>Bupivacaine 0.125%–fentanyl 3 μg ml⁻¹ (n=20)</th>
<th>Bupivacaine 0.125%–clonidine 0.6 μg ml⁻¹ (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>66 (57–77)</td>
<td>64 (31–85)</td>
<td>67 (54–82)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>73 (16)</td>
<td>81 (14)</td>
<td>73 (12)</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>14/6</td>
<td>15/5</td>
<td>15/5</td>
</tr>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>63 (9)</td>
<td>63 (11)</td>
<td>57 (12)</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction (%)</strong></td>
<td>25</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td><strong>Chronic pulmonary obstructive disease (%)</strong></td>
<td>15</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>30</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td><strong>Renal dysfunction (%)</strong></td>
<td>5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>70</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td><strong>Prior stroke (%)</strong></td>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of grafts</strong></td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Ischaemic time (min)</strong></td>
<td>16 (5)</td>
<td>18 (6)</td>
<td>17 (5)</td>
</tr>
<tr>
<td><strong>Intraoperative PaCO₂ at FiO₂=1 (kPa)</strong></td>
<td>23.5 (7.7)</td>
<td>19.6 (9.3)</td>
<td>18.7 (7.1)</td>
</tr>
<tr>
<td><strong>Intraoperative PaO₂ (kPa)</strong></td>
<td>5.5 (0.8)</td>
<td>5.3 (0.7)</td>
<td>5.1 (0.5)</td>
</tr>
</tbody>
</table>

The frequency of postoperative complications was not different between the three groups: one patient in each of groups B and BC suffered from postoperative myocardial infarction, no patients had postoperative infection there were no perioperative deaths. There was no significant difference in the incidence of atrial fibrillation: three patients in group B, six in group BF and four in group BC experienced postoperative atrial fibrillation which could be converted in all patients either pharmacologically or by synchronous defibrillation.

Side-effects related to the epidural analgesia were similar in three groups: 25% of patients in group B, 28% in group BF and 24% in group BC complained of paraesthesia in dermatomes T1 and C8. In all these patients, paraesthesia subsided on lowering the infusion rate of the equivalent solution. Eighteen of 20 patients in group B, 17 in group BF and 17 in group BC were awake, and all the others were sleepy but could easily be woken with verbal commands. No patients showed neurological signs or symptoms of epidural haematoma.

Immediate post-operative pain scores at rest were low and similar in groups B, BF and BC, respectively. Pain scores at 6 h, 24 h and 48 h after surgery remained low in the three groups and were not statistically different between groups (Fig. 3).

One patient in the fentanyl group complained of pruritus which began 48 h after initiation of epidural analgesia. The study solution was changed to plain bupivacaine.

There was no difference between groups in the incidence of nausea or vomiting. Three of the patients in each group required supplementary analgesia for leg pain.

**Discussion**

Postoperative analgesia after OPCAB using high TEA was very good with bupivacaine alone, bupivacaine with clonidine and bupivacaine with fentanyl. The addition of clonidine or fentanyl did not change significantly the quality.
of analgesia or the required rate of infusion of TEA. The addition of clonidine or fentanyl did not diminish the incidence of upper-extremity paraesthesia or change the rate of postoperative arrhythmias or the level of sedation.

To date, there has been no study comparing different epidural regimens for TEA in cardiac surgery. However, epidural regimens based on local anaesthetic alone or in combination with opioid or clonidine have been published separately for cardiac surgery. In all those studies, good to very good pain scores could be achieved. The excellent quality of postoperative analgesia with TEA using local anaesthetic alone might be one of the reasons why it was impossible in the present study to improve analgesia further by adding clonidine or fentanyl.

This study also focused on the rate of infusion and occurrence of side-effects such as sedation or paraesthesia in the upper extremities, which occur quite often in high TEA. Although all patients were informed about this possibility before surgery and the origin and nature of this phenomenon (the T1 is a common nerve supply of the superior sternal wound area and some areas of the arm) was explained to them, most patients still considered it a troubling side-effect.
creating anxiety about possible paralysis. However, the suggestion that the addition of either fentanyl or clonidine could allow infusion rates to be reduced and thus diminish the occurrence of this side-effect could not be proved by our findings.

Since both fentanyl and clonidine exercise general effects in terms of sedation, a simple examination of the state of awareness was used in all patients. All were well awake after extubation during the immediate recovery period (up to 6 h) and during the first 24 h of ICU stay, and no patient suffered from increased sedation during their hospital stay.

Clonidine is known as an antihypertensive drug which can cause hypotension and bradycardia. This phenomenon is also known for its intrathecal or epidural use.\textsuperscript{16–18} Ghignone and colleagues\textsuperscript{16} found reductions in heart rate, cardiac...
output, blood pressure and isovolaemic indices of contractility in anaesthetized dogs after epidural application of clonidine and postulated that these changes can be explained by a reduction of sympathetic outflow at the spinal cord and medulla oblongata levels as well as increased parasympathetic tone. However, our findings did not show a significant difference in haemodynamic stability between the groups. It could be that this effect is dose dependent, and higher doses of clonidine might have caused either hypotension or bradycardia.

High epidural analgesia is still considered by some anaesthesiologists as too risky for cardiac surgery. We have long used TEA in cardiac surgery, including cardiac surgery with cardiopulmonary bypass. The only recent risk calculation was published in 2000, and was based on all published cases of TEA in cardiac surgery. To date, there has been only one case of epidural haemaoma after cardiac surgery (aortic valve replacement). However, this haematoma was caused by inadvertent full heparinization after surgery, the application of antithrombotic agent and the retrieval of the catheter with a partial thromboplastin time (PTT) >80. It could well be that this was just a concomitant haematoma which had nothing to do with the catheter. In calculations by Ho and colleagues, the risk of epidural haematoma is 1:1500. Any further study published with TEA in cardiac surgery without haematoma will diminish the risk calculation. In addition, this is a risk calculated for cardiac surgery in general. The risk calculation for OPCAB should be different. First, the dose of heparin given is lower (150 IU kg$^{-1}$), only 1.5 times the dose used in vascular surgery where the use of TEA is well established. Second, one has to calculate the risk according to the probability of converting an OPCAB into on-pump CABG. The current percentage of OPCAB in all coronary artery bypass grafting in our setting is >95% with a conversion rate of <0.1%. Thus the risk of epidural haematoma should be significantly lower than 1:1500.

In our patients, there was no inadvertent sanguine puncture, all epidural catheters were inserted >1 h before heparin, we used the midline approach in all patients and all catheters were inserted with no more than three attempts. This pilot study was designed to calculate sample size for future studies. Before the study, we theorized that the supplement of clonidine or fentanyl would not significantly increase the analgesia since most patients were already pain free with bupivacaine alone. This was confirmed in this study. Possible reductions in epidural infusion rate or significant differences in side-effects, such as paraesthesia, were also not found. We conclude that TEA using bupivacaine 0.125% alone, bupivacaine 0.125% with fentanyl 3 μg ml$^{-1}$ or bupivacaine 0.125% with clonidine 0.6 μg ml$^{-1}$ provides excellent postoperative analgesia after OPCAB. The addition of either clonidine or fentanyl does not change the haemodynamic stability, the rate of epidural infusion, the level of sedation or the rate of paraesthesia.

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