Safety and efficacy of postoperative epidural analgesia

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Effective analgesia for postoperative pain relief after major surgery has been a practical proposition with epidural administration of local anaesthetic (LA) and opioid drugs since the early 1980s. Although epidural administration is perceived by 80% of UK anaesthetists as the ideal analgesic technique for upper abdominal surgery, there are many patients undergoing major surgery who do not receive this form of analgesia. In a recent survey of UK practice, only 15% of patients undergoing abdominal surgery had epidural analgesia in the 12 hospitals sampled. The main factor which has limited the use of epidural analgesia has been the difficulty in making a reasonable risk/benefit analysis about the technique, which has resulted in clinicians constantly asking whether epidurals are effective for postoperative pain relief and whether the technique is safe.

This review considers the efficacy and safety of epidural analgesia in patients recovering from major surgery and is based on a computerized search of the literature from 1976 to 2000 (EMBASE/Medline). The final section will deal with the organizational issues which need to be considered to maximize efficacy and safety and is based on the authors’ joint experience of supervising acute pain services (APS) in New Zealand and the UK; these services have been responsible for pain relief in over 20 000 patients nursed on general postoperative wards.

Efficacy

Efficacy has been defined as ‘the ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances’. It is important to bear this definition in mind as the published results on efficacy are usually based on expert practice in optimal conditions. The difficulties in making this transition from the controlled setting of a clinical trial to routine clinical practice have been highlighted by the results of recently published audits, which have demonstrated a failure rate of 30–50% for epidural analgesia.

The ideal epidural analgesic technique for major surgery would provide effective pain relief with minimal side effects and high levels of patient satisfaction. It would also obviate central sensitization and pain-induced organ dysfunction, leading to improved outcome. This topic is covered in the accompanying review in this issue on postoperative pain relief and surgical outcome. It is self-evident that the primary measure of efficacy of any analgesic regimen is pain relief. However, pain is a complex, subjective experience which has proved difficult to measure in a reproducible way. Early studies of postoperative analgesia relied on measurement of pain scores at rest and surrogate measures, such as respiratory spirometry. Reliance on measuring pain scores at rest resulted in failure to identify those techniques which allowed patients to mobilize and cough effectively, i.e. techniques that provided dynamic pain relief.

Total dynamic pain relief, i.e. complete absence of pain on moving and coughing after major upper abdominal surgery, can be produced in the intensive care environment by the use of large doses of opioid and LA drugs. This is an unrealistic aspiration for a ward-based analgesic technique, as high doses of these drugs are associated with an unacceptable incidence of hypotension and respiratory depression. A more realistic approach is to measure pain on movement or coughing and to aim for a patient who can mobilize, take deep breaths and cough effectively and who scores 3 or less out of 10 on a visual analogue or numerical rating scale measured on movement. Although many studies have used spirometric assessment as an outcome measure, a recent meta-analysis cast doubt on the validity of using these techniques as a surrogate measure of the efficacy of epidural analgesia.

The difficulty with interpreting the available data on efficacy is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space before or after surgical incisions for a wide variety of operations. In this section of the review we consider the evidence from randomized controlled trials (RCTs) in which dynamic pain relief was an outcome measure, in order to assess the factors which modify the effectiveness of
epidural analgesia such as the choice of drugs, the site of epidural insertion in relation to the surgical incision and the timing and method of drug delivery.

### Choice of drug

#### Local anaesthetic

Epidural LA drugs administered alone have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block and the unacceptable incidence of motor blockade and hypotension. In a study of patients undergoing thoracic surgery, despite the infusion of bupivacaine 37.5–50 mg h\(^{-1}\) via a thoracic epidural, 30% of patients required opioid supplementation for inadequate analgesia and 80% had significant hypotension. Similar results were also found when bupivacaine 24–45 mg h\(^{-1}\) or ropivacaine 10–30 mg h\(^{-1}\) was infused epidurally after upper abdominal surgery. In an opioid-free postoperative analgesic regimen, infusion rates of bupivacaine 10–12.5 mg h\(^{-1}\) supplemented by systemic non-steroidal anti-inflammatory drugs were found to be ineffective in lower abdominal surgery.

#### Opioids

The use of epidural analgesia for pain relief was revolutionized by the use of epidural opioids after the discovery of opioid receptors in the dorsal horn of the spinal cord. Opioids have both presynaptic and postsynaptic effects in the dorsal horn and affect the modulation of nociceptive input but do not cause motor or sympathetic blockade.

Despite the initial enthusiasm for epidural opioids, with their promise of profound, long-lasting analgesia with minimal side-effects, there is still considerable debate about their place in postoperative pain management. Opioid-based techniques have been used widely in the USA and Australia and are usually based on bolus administration of drugs such as morphine, diamorphine and pethidine or the continuous infusion of lipophilic opioids such as fentanyl or sufentanil.

Although bolus epidural opioids may produce longer-lasting analgesia with smaller doses than intermittent i.m. opioids, there is less convincing evidence that they improve the quality of analgesia when the technique is compared to i.v. patient-controlled anaesthesia (PCA). The RCTs of continuous infusions of lipophilic opioids compared with i.v. or patient-controlled i.v. opioids in which pain on coughing or movement was assessed are shown in Table 1.

The evidence for a spinal rather than a systemic action of fentanyl is conflicting. Although significant differences in efficacy were not demonstrated when fentanyl or sufentanil were administered epidurally or i.v. after knee or major abdominal surgery, epidural fentanyl produced more effective dynamic pain relief than i.v. PCA morphine or fentanyl in lower abdominal and thoracic surgery. In the majority of studies in which plasma concentrations have been measured, there was no significant difference in plasma concentrations between the two routes of administration. Furthermore, plasma concentrations of

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**Table 1** RCTs comparing lipophilic opioid epidural infusions with intravenous or patient-controlled intravenous opioids with dynamic pain relief as an outcome measure. NS difference=no significant difference; PCEA=patient controlled epidural anaesthesia

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Epidural regimen</th>
<th>Site of insertion</th>
<th>Type of surgery</th>
<th>Comparator</th>
<th>Dynamic pain relief compared with control group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>20</td>
<td>Fentanyl infusion 100 µg h(^{-1})</td>
<td>Lumbar</td>
<td>Knee</td>
<td>i.v. fentanyl infusion100 µg h(^{-1})</td>
<td>NS difference</td>
<td>NS difference in plasma concentrations</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>Fentanyl infusion 1 µg kg(^{-1}) h(^{-1})</td>
<td>Lumbar</td>
<td>Lower abdominal</td>
<td>i.v. PCA morphine</td>
<td>Epidural more effective</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>36</td>
<td>Fentanyl infusion 50 µg h(^{-1})</td>
<td>Thoracic</td>
<td>Thoracic</td>
<td>i.v. PCA morphine</td>
<td>Epidural more effective</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>Fentanyl PCEA 20 µg bolus</td>
<td>Lumbar</td>
<td>Lower abdominal</td>
<td>I.v. PCA fentanyl 20 µg bolus</td>
<td>Epidural more effective at 8–12 h</td>
<td>Reduced fentanyl consumption in the epidural group</td>
</tr>
<tr>
<td>28</td>
<td>32</td>
<td>Alfentanil PCEA 250 µg bolus</td>
<td>Thoracic</td>
<td>Major abdominal</td>
<td>i.v. alfentanil PCA 250 µg bolus</td>
<td>NS difference</td>
<td>Reduced alfentanil consumption in the epidural group</td>
</tr>
<tr>
<td>107</td>
<td>50</td>
<td>Sufentanil infusion 0.2 µg kg(^{-1}) h(^{-1})</td>
<td>Lumbar</td>
<td>Major abdominal</td>
<td>i.v. sufentanil 0.2 µg h(^{-1})</td>
<td>NS difference</td>
<td>NS difference in opioid dose</td>
</tr>
<tr>
<td>38</td>
<td>84</td>
<td>Fentanyl PCEA 20 µg bolus</td>
<td>Lumbar</td>
<td>Lower abdominal</td>
<td>I.v. PCA morphine</td>
<td>Epidural more effective for 21 h</td>
<td></td>
</tr>
</tbody>
</table>

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fentanyl were usually above the minimum effective analgesic concentration of 0.23–1.18 (mean 0.63) ng ml$^{-1}$ for i.v. fentanyl.\textsuperscript{62}

On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route appear to be marginal, or unproven in the case of upper abdominal surgery, and in many situations will not outweigh the risks of the more invasive route of administration.

**Opioid–local anaesthetic combinations**

Epidural infusions of LA–opioid combinations are the most commonly used epidural technique in the UK\textsuperscript{34} and Australia,\textsuperscript{35} being used by 97% of anaesthetists who use the technique. Their use is based on the clinical observation that the combination of LA and opioid drugs limits the regression of the sensory block seen with LAs alone\textsuperscript{65} and improves the quality of dynamic pain relief.\textsuperscript{52} However, there are major regional and national differences in the choice of opioid and LA drugs used for postoperative epidural analgesia. In a UK survey, 40% of anaesthetic departments used diamorphine and 51% used fentanyl in combination with LA drugs.\textsuperscript{129}

The RCTs comparing LA–opioid combinations and LA or opioids alone with dynamic pain relief as an outcome measure are shown in Table 2.

The majority of studies show that the use of a mixture of LA and opioid is associated with significantly better dynamic pain relief after lower or upper abdominal,\textsuperscript{39,52,101–119,145–168} orthopaedic,\textsuperscript{79,87} and thoracic\textsuperscript{95,115,168} surgery than the components of the mixture infused alone.

However, in a within-patient crossover study, Torda and colleagues could not demonstrate any difference in efficacy between bolus doses of fentanyl 50 μg, bupivacaine 50 mg or a mixture of both.\textsuperscript{157} Similarly, Mahon and colleagues were unable to demonstrate any improvement in efficacy by adding 0.1–0.2% bupivacaine to fentanyl 10 μg ml$^{-1}$ after the first 2 h after thoracotomy.\textsuperscript{103}

Epidural analgesia with LA–opioid combinations has been shown to be significantly better than i.v. PCA morphine in providing dynamic pain relief after major abdominal surgery.\textsuperscript{18,97,104,113} (Table 3).

Is there an optimal combination of opioid and LA for epidural analgesia? Despite differences in epidural to systemic potency between different opioid drugs, there are no RCTs, with dynamic pain relief as an outcome measure, which compare the efficacy of different epidural LA–opioid combinations. However, it is clear that the co-administration of LA with opioid significantly reduces the opioid requirement of all opioids studied. Many of the early studies used a fentanyl concentration of 10 μg ml$^{-1}$ on the basis of a dose-finding study of epidural fentanyl used alone.\textsuperscript{165} In a subsequent dose-finding study, in which fentanyl was combined with 0.125% levobupivacaine, an optimal concentration of 4 μg ml$^{-1}$ was recommended.\textsuperscript{145} Similarly, reduced concentrations of less lipophilic opioids, such as 50 μg ml$^{-1}$ of morphine and diamorphine,\textsuperscript{101} have been shown to be effective.

The optimal dose of the LA component of the epidural mixture is becoming clearer. In two postoperative studies in which pain relief on movement\textsuperscript{77,152} was not significantly better in the combination group, the concentration of bupivacaine used was 0.1% or less and it was delivered as patient-controlled epidural anaesthesia (PCEA) without a background infusion. A dose of 4–12 mg h$^{-1}$ of bupivacaine, when combined with morphine 50 μg ml$^{-1}$,\textsuperscript{42} diamorphine 80 μg ml$^{-1}$,\textsuperscript{101} fentanyl 10 μg ml$^{-1}$,\textsuperscript{119} sufentanil 1 μg ml$^{-1}$,\textsuperscript{168} and administered via a thoracic epidural catheter, has been shown to provide effective dynamic pain relief. The addition of opioid, therefore, significantly reduces the hourly requirement of bupivacaine from 25–45 mg h$^{-1}$ when used alone.\textsuperscript{33,108,131}

In a recent study, in which a direct search procedure was used to determine the optimal combinations of thoracic epidural bupivacaine and fentanyl after major abdominal surgery, the two most effective regimens were bupivacaine 8 mg h$^{-1}$ and fentanyl 30 μg h$^{-1}$ or bupivacaine 13 mg h$^{-1}$ and fentanyl 25 μg h$^{-1}$; both infused at 9 ml h$^{-1}$.

Although the doses of LA are small, it is likely that the newer LA drugs, levobupivacaine and ropivacaine, will be used increasingly because of their improved safety margin and, in the case of ropivacaine, the potential advantage of less motor blockade. Although this latter advantage appears to be relevant at the higher concentrations used for intraoperative analgesia, the differences between the drugs are less marked at the dilute concentrations used for postoperative analgesia. In a study after major abdominal surgery, 0.2% ropivacaine was not significantly different, in terms of analgesia or motor blockade, from 0.125% bupivacaine when both were combined with fentanyl 2 μg ml$^{-1}$.\textsuperscript{14}

**Site of insertion**

A meta-analysis of studies comparing the thoracic or lumbar approaches to the epidural space for opioids alone failed to demonstrate any significant improvement in analgesia when the thoracic approach was used.\textsuperscript{9}

There are no RCTs comparing LA–opioid combinations administered via the thoracic or lumbar approaches. Nevertheless, the use of the thoracic rather than the lumbar approach to the epidural space has been one of the major changes in anaesthetic practice over the last 20 yr and has been used in the majority of studies that have demonstrated improved dynamic pain relief.\textsuperscript{39,42,95,97,101,104,113,115,119,145,146,168} This technique has a number of potential benefits when used for the administration of LA–opioid mixtures. The thoracic approach facilitates the incision-congruent administration of lipophilic opioids in small doses and minimizes motor and sympathetic blockade of the lower.
<table>
<thead>
<tr>
<th>Reference No.</th>
<th>No. of patients</th>
<th>Epidural regimen</th>
<th>Type of surgery/site of epidural</th>
<th>Comparator</th>
<th>Dynamic pain relief compared with control group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>146</td>
<td>22</td>
<td>Morphine 500 µg h⁻¹</td>
<td>Upper abdominal/thoracic</td>
<td>0.5% Bupivacaine 25 mg h⁻¹</td>
<td>Combination more effective</td>
<td>2 patients withdrawn because of hypotension or respiratory depression</td>
</tr>
<tr>
<td>42</td>
<td>24</td>
<td>Morphine 200 µg h⁻¹</td>
<td>Major abdominal/thoracic</td>
<td>Morphine 200 µg h⁻¹</td>
<td>Combination more effective</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>64</td>
<td>Morphine 200 µg h⁻¹</td>
<td>Major abdominal/thoracic</td>
<td>Morphine 200 µg h⁻¹</td>
<td>Combination more effective</td>
<td>Less supplementary analgesia required</td>
</tr>
<tr>
<td>101</td>
<td>40</td>
<td>Diamorphine 250–600 µg h⁻¹</td>
<td>Upper abdominal/thoracic</td>
<td>Diamorphine 250–600 µg h⁻¹</td>
<td>Combination more effective</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>66</td>
<td>Pethidine 1 mg ml⁻¹</td>
<td>Thoracic/thoracic</td>
<td>Pethidine</td>
<td>NS difference</td>
<td>NS difference in drug consumption</td>
</tr>
<tr>
<td>119</td>
<td>90</td>
<td>Fentanyl 40 µg h⁻¹</td>
<td>Major abdominal/thoracic</td>
<td>Fentanyl 40 µg h⁻¹</td>
<td>Combination more effective for the first 24 h</td>
<td></td>
</tr>
<tr>
<td>157</td>
<td>24</td>
<td>Fentanyl 50 µg + bupivacaine 12.5 or 25 mg bolus doses</td>
<td>Major abdominal surgery/thoracic</td>
<td>Fentanyl 50 µg</td>
<td>NS difference</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>24</td>
<td>Fentanyl PCEA 0.01–0.1% bupivacaine 10 ml h⁻¹</td>
<td>Thoracic</td>
<td>Fentanyl PCEA</td>
<td>Combination more effective</td>
<td>Optimal bupivacaine dose 5 mg h⁻¹</td>
</tr>
<tr>
<td>37</td>
<td>60</td>
<td>Fentanyl 2 µg ml⁻¹</td>
<td>Lower abdominal/lumbar</td>
<td>Fentanyl 4 µg ml⁻¹ or 0.15% bupivacaine PCEA</td>
<td>NS difference</td>
<td>Significantly reduced fentanyl or bupivacaine doses when combination used</td>
</tr>
<tr>
<td>103</td>
<td>106</td>
<td>Fentanyl 50–100 µg h⁻¹</td>
<td>Thoracic/thoracic</td>
<td>Fentanyl 50–100 µg h⁻¹</td>
<td>NS difference after the first 2 h</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>68</td>
<td>Fentanyl 4 µg ml⁻¹</td>
<td>Arthroplasty/lumbar</td>
<td>Fentanyl 4 µg ml⁻¹ or 0.125% levobupivacaine PCEA</td>
<td>Combination more effective</td>
<td>NS difference in opioid doses</td>
</tr>
<tr>
<td>145</td>
<td>259</td>
<td>Fentanyl 1–4 µg ml⁻¹</td>
<td>Major abdominal/thoracic</td>
<td>Ropivacaine 0.2%</td>
<td>Combination more effective</td>
<td>Optimal fentanyl dose 4 µg ml⁻¹</td>
</tr>
<tr>
<td>115</td>
<td>50</td>
<td>Sufentanil 0.8 µg ml⁻¹</td>
<td>Thoracic/thoracic</td>
<td>Sufentanil 0.8 µg ml⁻¹ or 0.125% bupivacaine 5–10 ml h⁻¹</td>
<td>Combination more effective</td>
<td>0.125% bupivacaine ineffective</td>
</tr>
<tr>
<td>168</td>
<td>100</td>
<td>Sufentanil 1 µg ml⁻¹</td>
<td>Thoracic abdominal</td>
<td>0.17% Bupivacaine</td>
<td>Combination more effective</td>
<td>Less supplementary analgesia required</td>
</tr>
<tr>
<td>79</td>
<td>30</td>
<td>Sufentanil 5–9 µg h⁻¹</td>
<td>Orthopaedic/lumbar</td>
<td>0.1% Ropivacaine</td>
<td>Combination more effective</td>
<td>Less supplementary analgesia required</td>
</tr>
</tbody>
</table>
limbs. Although initially seen as a disadvantage because of the attendant hypotension, the importance of a controllable degree of sympathetic blockade in the attenuation of the adverse adrenergic effects on the cardiovascular and gastrointestinal systems is now being realized.128

Pre- or post-incisional epidural analgesia

In order to see a pre-emptive effect with an analgesic intervention, it is necessary to provide good analgesia with inhibition of central sensitization extending into the postoperative period.169 This may explain the lack of pre-emptive effect when an epidural is given before or after surgical incision and analgesia is provided in the postoperative period by i.v. PCA morphine51 126 (Table 4).

However, no significant difference in dynamic pain relief was seen when bupivacaine and morphine were given before and after incision and continued into the postoperative period31 or when bupivacaine alone was given followed by PCEA with fentanyl and bupivacaine.2 Two recent studies have demonstrated a pre-emptive effect. Using a mixture of ketamine, bupivacaine and morphine, Wu and colleagues demonstrated a statistically significant improvement in analgesia in the pre-incisional group after upper abdominal surgery during the first postoperative day.171 However, the differences in clinical terms were marginal as patients in both groups had good dynamic pain relief. Patients recovering from radical prostatectomy, all of whom had an aggressive postoperative epidural analgesic regimen, had significantly less pain in hospital and 9.5 weeks later if they had had epidural fentanyl or bupivacaine administered before surgical incision.61 Although this is one of the few studies demonstrating a clinically significant pre-emptive effect, its conclusions are limited by the fact that pain scores were measured at rest.

Method of drug delivery

Bolus versus infusion

Postoperative epidural analgesia is usually administered via a continuous infusion to maintain a level of analgesia and to minimize the cardiovascular and respiratory effects of bolus doses of LA and opioid respectively. Intermittent bolus dosing of LA alone has been shown to minimize block regression and marginally improve analgesia compared with a continuous infusion of the same hourly dose in patients undergoing lower abdominal surgery.48 However, there was no difference in pain scores on coughing between the two groups, and this technique has not been studied in patients receiving epidural LA-opioid combinations for upper abdominal surgery.

PCEA with or without a background infusion

Allowing patients to have control of their analgesia has become an important principle in acute pain management. Although the role and optimal regimen of PCEA after major surgery have not yet been fully clarified, the technique has the practical safety advantage of permitting bolus doses which do not require to be mixed on the ward. The importance of a background infusion when using an LA-opioid combination was emphasized in a recent study in patients recovering from gastrectomy when PCEA alone was shown to be less effective in reducing pain on coughing than PCEA with a background infusion.86

Choice of adjuvants

In addition to LA agents and opioids, a number of agents have been used as adjuvants to improve the efficacy of epidural analgesia. These include ketamine [antagonist of NMDA (N-methyl-D-aspartate)], midazolam [agonist of GABA (γ-aminobutyric acid)], clonidine (α2 agonist) and adrenaline.

The results of RCTs of adjuvant agents added to LA-opioid combinations are shown in Table 5.
Although ketamine 400 μg ml⁻¹, used as an adjuvant to a low-dose epidural infusion of morphine, bupivacaine and adrenaline, enhanced dynamic pain relief,30 concerns have been expressed about the lack of data on the potential neurotoxicity of ketamine.173 Similarly, enthusiasm for the improved efficacy seen with the addition of clonidine 18–20 μg h⁻¹ to thoracic epidural analgesia118 109 is tempered by concerns about the increased incidence of hypotension and the increased level of surveillance needed. Although midazolam and verapamil have been used with bupivacaine, there are no data on their use as adjuvants to continuous epidural analgesia with LA–opioid combinations.

The addition or removal of adrenaline to a low-dose epidural mixture of bupivacaine and fentanyl has been investigated by Niemi and Breivik in a double-blind crossover study after major surgery.116 The use of epinephrine was associated with minimal regression of the sensory block, markedly improved pain relief on coughing and reduced serum fentanyl concentrations. Despite concerns about the safety of adding vasoconstrictors to epidural mixtures, Breivik and colleagues have used this triple-component epidural mixture in over 6000 patients with apparent safety.20

### Safety

There are a number of complications that can result from epidural analgesia, some of which are of major concern because of their potential to cause permanent neurological damage. Such adverse effects can be related to needle and catheter insertion, the presence of the catheter in the epidural space or the drugs infused, including drug errors. The introduction of Acute Pain Services has enabled early recognition of these diverse and, in some cases, extremely rare complications so that corrective action can be taken to prevent permanent harm.

### Incidence of serious neurological complications due to epidural analgesia

Because of the rarity of permanent neurological damage resulting from epidural analgesia, it is difficult to estimate its incidence. In a combined series of more than 50 000

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**Table 4** RCTs of pre-versus post-incisional administration of epidural analgesia with dynamic pain relief as an outcome measure. NS difference = no significant difference

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Epidural regimen</th>
<th>Site of insertion</th>
<th>Type of surgery</th>
<th>Postoperative analgesia</th>
<th>Dynamic pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>40</td>
<td>0.5% bupivacaine 20 ml</td>
<td>Lumbar</td>
<td>Lower abdominal</td>
<td>PCA i.v. morphine</td>
<td>NS difference</td>
</tr>
<tr>
<td>126</td>
<td>25</td>
<td>0.5% bupivacaine 15 ml + fentanyl 50 μg</td>
<td>Lumbar</td>
<td>Lower abdominal</td>
<td>PCA i.v. morphine</td>
<td>NS difference</td>
</tr>
<tr>
<td>141</td>
<td>32</td>
<td>0.75% bupivacaine 7 ml + morphine 2 mg</td>
<td>Thoracic</td>
<td>Major abdominal</td>
<td>Epidural morphine + bupivacaine</td>
<td>NS difference</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>bupivacaine 8 ml + epinephrine</td>
<td>Thoracic</td>
<td>Thoracic</td>
<td>PCEA fentanyl + bupivacaine + epinephrine</td>
<td>NS difference</td>
</tr>
<tr>
<td>171</td>
<td>60</td>
<td>Ketamine + morphine + bupivacaine</td>
<td>Thoracic</td>
<td>Upper abdominal surgery</td>
<td>Ketamine + morphine + bupivacaine twice per day</td>
<td>Significantly better in the pre-incisional group</td>
</tr>
</tbody>
</table>

**Table 5** RCTs of adjuvant therapy plus LA–opioid combinations with dynamic pain relief as an outcome measure

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Epidural regimen</th>
<th>Site of insertion</th>
<th>Type of surgery</th>
<th>Adjuvant</th>
<th>Dynamic pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>91</td>
<td>PCEA morphine 20 μg ml⁻¹ + 0.08% bupivacaine + epinephrine 4 μg ml⁻¹</td>
<td>Thoracic</td>
<td>Major surgery</td>
<td>Ketamine 400 μg ml⁻¹</td>
<td>Better in the ketamine group</td>
</tr>
<tr>
<td>116</td>
<td>24</td>
<td>Fentanyl 20 μg h⁻¹ + 0.1% bupivacaine 10 mg h⁻¹</td>
<td>Thoracic</td>
<td>Major abdominal and thoracic</td>
<td>Epinephrine 2 μg ml⁻¹</td>
<td>Better in the epinephrine group</td>
</tr>
<tr>
<td>109</td>
<td>24</td>
<td>Morphine 100 μg h⁻¹ + bupivacaine 5 mg h⁻¹</td>
<td>Thoracic</td>
<td>Lower abdominal</td>
<td>Clonidine 18.75 μg h⁻¹</td>
<td>Better pain relief but more hypotension</td>
</tr>
<tr>
<td>118</td>
<td>100</td>
<td>Fentanyl 10 μg h⁻¹ + 0.125% bupivacaine 7.5 mg h⁻¹ + PCEA fentanyl</td>
<td>Thoracic</td>
<td>Lower abdominal</td>
<td>Clonidine 2, 3 or 4 μg ml⁻¹ 5 ml h⁻¹</td>
<td>Better pain relief with clonidine 20 μg h⁻¹ but more hypotension</td>
</tr>
</tbody>
</table>
epidural anaesthetics, only three patients suffered permanent leg weakness (0.006%).

A retrospective study of 170 000 epidural anaesthetics in Finland over 10 yr and of the resulting claims for compensation revealed nine serious complications (0.005%): one case of paraparesis, one case of permanent cauda equina syndrome, one case of peroneal nerve paresis, one case of neurological deficit, two bacterial infections, two acute toxic reactions related to the anaesthetic solutions and one overdose of epidural opioid.

However, the incidence may be underestimated by such retrospective reviews. A prospective French study, involving 30 413 epidurals inserted over a 5-month period, revealed an incidence of severe complications of 0.04%: three cardiac arrests, four convulsions and six neurological injuries.8 Although Giebler and colleagues found no permanent neurological deficit in a study of 4185 epidurals, the upper limit of his 95% confidence interval gives a predicted maximal risk for permanent neurological complications of 0.07%.56 Dahlgren and Tornebrandt similarly reported an incidence of persistent neurological deficit of 0.03% after 9232 epidurals;13 this is 10 times the risk given by Kane60 and by Aromaa and colleagues.

However, on many occasions the association between epidural anaesthesia/analgesia and serious neurological sequelae is only a temporal one and might be inappropriate to be causal, as described in various case reports.

**Adverse events due to the insertion of needle and catheter**

**Dural puncture**

Dural puncture occurs in 0.32–1.23% of epidural placements and can result in the development of a postdural puncture headache. Rarely, subdural haematoma that can result in neurological deterioration has been described after dural puncture,57 75 its incidence may be less with loss of resistance to saline than to air.46 81 130 There is also a risk of pneumocephalus if air is used,105 which can result in serious complications.93 127 150 The use of saline may again help to reduce the incidence of this and other complications that have been associated with the use of air, notably spinal cord and nerve root compression and venous air embolism.76 78 134 148 In addition, accidental pleural puncture during epidural catheter insertion has been described,57 175 as has haemothorax.74

**Direct trauma**

Direct trauma to the spinal cord or peripheral nerves due to the needle or catheter is extremely rare, but has been reported. Epidural catheterization is most frequently performed in the awake patient to avoid this risk of neurological damage. This problem, which was highlighted in a recent case report,22 is still being debated.84 In support of epidural insertion in the anaesthetized patient, a recent study involving the placement of cerebrospinal fluid drainage needles and catheters in 530 anaesthetized patients undergoing neurosurgery reported no cases of nerve injury in the immediate postoperative period or within 1 yr of surgery.63

**Transient neuropathy**

Transient neuropathy with eventual full recovery occurs more commonly but is still relatively infrequent; a recent large prospective multicentre series involving 30 413 epidural anaesthetics reported five cases of radiculopathy (0.016%), over 50% recovering completely within 3 months.8 This incidence is similar to previously published large studies on transient neuropathy: 4 out of 17 439 patients (0.023%) and 0.013% from a retrospective study of 1 304 214 epidurals.172 Other much smaller studies report an incidence of 0.24–0.56%,59 138 A recent paediatric study found an incidence of up to 3%, but this involved small numbers of patients.121 After certain operations, such as tibial fracture fixation, epidural analgesia has been implicated in a higher incidence of neurological complications.73 However, a retrospective study demonstrated no significant association between the development of peroneal nerve palsy after total knee replacement and the use of postoperative epidural analgesia.

**Adverse events due to the presence of an indwelling catheter in the epidural space**

**Spinal haematoma**

Puncture of epidural vessels during catheter placement occurs during 3–12% of attempts.143 However, the subsequent development of a spinal haematoma causing neurological damage is a rare complication. If not detected and treated early, it results in irreversible paraplegia. The incidence of clinically apparent epidural haematoma is unknown, as any study attempting to quantify it would have to involve an enormous number of patients. However, its occurrence does seem to be increasing, possibly as a result of increased use of regional anaesthesia in combination with altered coagulation [in particular low-molecular weight heparin (LMWH)] or of better reporting of the complication.

The risk of developing a spinal haematoma can be quantified only by either studying large numbers of routine or at-risk patients or collecting case reports of spinal haematoma after epidural blockade. The reported incidence varies greatly between studies. Vandermeulen and colleagues combined 18 studies involving 200 000 patients who received epidural analgesia and found no incidence of epidural haematoma.161 In a review including 13 case series that involved >850 000 epidurals, there were only three cases of haematoma (0.0004%).52 At the other extreme, three cases of epidural haematoma were reported after 9232 (0.03%) epidural insertions;43 an even higher incidence, of two cases out of 1014 (0.2%) insertions, has also been reported.144 On the basis of all available information, Tryba...
has given the best estimate for the risk of a spinal haematoma after epidural analgesia to be 1:150 000 at the upper 95% confidence interval.158

Examination of case reports of spinal haematoma has revealed potential risk factors, notably haemostatic abnormalities and/or anticoagulation, in particular the timing of catheter insertion and removal in relation to the administration of anticoagulants. In 61 cases of spinal haematoma associated with epidural/spinal anaesthesia, 42 (68%) of them had evidence of haemostatic abnormality: 30 had received heparin and 12 had evidence of coagulopathy or were treated with antiplatelet agents, thrombolysis or anticoagulants.161 Forty-six of these had undergone epidural anaesthesia, 32 with the use of an epidural catheter. In nearly 50% of these 32 patients, the spinal haematoma occurred immediately after removal of the catheter, nine being removed when heparin concentrations were therapeutic. This demonstrates that development of a haematoma is not just related to insertion but also (of equal importance) to removal of the epidural catheter. Overall, 87% of epidural haematomas were related to some haemostatic abnormality or procedure difficulty. Literature concerning obstetric patients revealed 17 cases of haematoma after epidural catheter insertions, of which 14 (82%) had a bleeding diathesis.135

However, three studies involving over 5000 systemically anticoagulated patients and one study of 805 patients taking antiplatelet medication who received central neuraxial blockade described no cases of spinal haematoma.10 70 117 123 Furthermore, four studies, involving intraoperative high-dose heparin during cardiac surgery in 776 adult patients and 234 paediatric patients who received central neuraxial blockade, failed to demonstrate any spinal haematoma formation, provided there were no other risk factors.102 121 136 160

The situation has changed dramatically with the introduction of LMWH as routine thromboembolic prophylaxis. A subsequent surge of epidural haematomas has ignited a very complex debate.67 For detailed current recommendations, the reader is directed to a recent review by Horlocker and Wedel.59 This review can be summarized as follows.

**Oral anticoagulation.** Catheter placement/removal should not be performed in fully anticoagulated patients. Epidural insertion is relatively safe, if low-dose warfarin (3–5 mg day–1) is started after catheter insertion (192 patients).71 An international normalized ratio (INR) of <1.4 at the time of catheter removal resulted in no case of spinal haematoma (459 patients).170

**Intravenous and subcutaneous standard heparin.** Systemic heparinization is safe for vascular surgery, if administered 60 min after catheter placement if coagulation is closely monitored and if the catheter is removed when circulating heparin concentrations are low.123 Low-dose subcutaneous heparin in combination with epidural analgesia is safe—there were only three cases of spinal haematoma in the literature and none in a review of more than 5000 patients.143

**LMWH.** At least 40 cases of spinal haematoma have been reported in the USA with neuraxial anaesthesia under LMWH prophylaxis.68 These were probably related to intraoperative or early postoperative administration, a twice-daily dosing schedule and concomitant antiplatelet therapy in the USA, as the European experience, with adherence to strict guidelines, is quite different. The worst incidence of spinal haematoma has been estimated at 1 in 3100 cases with continuous epidural analgesia under LMWH cover in the USA.140 New recommendations follow the European guidelines, recommending 24-hourly dosing and a 12-h interval between LMWH injection and insertion or removal of the catheter.

**Antiplatelet medications.** It is relatively safe to insert an epidural whilst the patient is receiving antiplatelet medication; this is supported by several large studies involving obstetric and surgical patients.5 72 No increased incidence of bloody tap was observed during epidural insertion in 1000 patients on antiplatelet medication, suggesting no difference in traumatic needle/catheter placement.70

**Infection**

Infection can be introduced into the epidural space from an exogenous source via contaminated equipment or drugs, or from an endogenous source, leading to bacteraemia, which seeds to the insertion site. Alternatively, the catheter can act as a wick through which infection tracks down from the entry site on the skin to the epidural space. Infection can result in meningitis (if the dura is breached) or epidural abscess formation, resulting in cord compression. It has been demonstrated that the spread of streptococci from the anaesthetist’s buccal mucosa can cause epidural infections.139 However, facemasks have not been shown to reduce the incidence of neuraxial infections.

Serious neuraxial infections after epidural anaesthesia have been reported as being rare. A review of 50 000 epidural anaesthetics did not show a single epidural or intrathecal infection80 and, more recently, Dahlgren and Tornebrandt reported no cases of epidural abscess out of 9232 epidural insertions.43 However, more recent, smaller studies cite the incidence as being closer to 1:10 000. A prospective Danish study, involving 17 372 epidural catheters, reported the incidence of epidural abscess to be 1:1930 (0.05%).163 other studies giving similar figures of 2:13 000 and 2:2000.84 135 The findings of the Danish study suggest that patients with epidural abscess had a longer mean catheterization time than the population mean, the majority of such patients were immunocompromised by one or more complicating diseases (malignancy, diabetes, multiple trauma, chronic obstructive respiratory disease) and perioperative anticoagulant therapy was involved in most cases.163 There were no reports of abscess formation in patients with catheters in situ for 2 days or less. Predominance of immunocompromised patients has also
been found in previous studies.\textsuperscript{47} \textsuperscript{82} The risk of persistent neurological deficit from an epidural abscess is almost 50%, which may be explained by the long period from diagnosis of an epidural abscess to intervention;\textsuperscript{163} this outcome has not improved since the period 1947–1974.\textsuperscript{85}

Epidural analgesia in patients with known systemic or localized infection remains controversial. Many anaesthetists have considered sepsis to be a relative contraindication for epidural anaesthesia. It is generally recommended that epidural catheterization should not be performed in patients with untreated bacteraemia, unless there is an overwhelming reason to do so.\textsuperscript{69} Jakobsen and colleagues, in a retrospective study of 69 patients with localized skin infections who underwent repeated epidural catheterization, reported no signs or symptoms of neuraxial infection.\textsuperscript{77} However, another study reported three neuraxial infections related to epidural catheterization in patients with localized infections.\textsuperscript{43} Small numbers in the studies make it difficult to provide recommendations.

Any patient with local or systemic infection is potentially at risk of developing neuraxial infection; extreme vigilance must be maintained in the monitoring and detection of epidural infection. There should be careful selection of patients currently responding to antibiotic treatment of their sepsis for which epidural analgesia is proposed. Also, the potential unproven risk of neuraxial infection after intraoperative transient bacteraemia during an obstetric or urological procedure should be considered. However, short-term catheterization in these patients is probably safe.\textsuperscript{69}

\textit{Catheter migration}

After initial placement of the epidural catheter in the epidural space, the tip of the catheter can move intrathecally. Similarly, i.v. migration can occur. Both must be considered before any bolus dose is administered via the epidural catheter by careful aspiration; a test dose of LA containing epinephrine can also provide evidence of i.v. migration by producing a transient tachycardia. These techniques, and the use of low-dose LA–opioid infusions, may help to prevent dramatic complications, such as total spinal anaesthesia with possible neurotoxicity\textsuperscript{90} and seizures.\textsuperscript{15} \textsuperscript{107} \textsuperscript{147} Unintentional subdural catheter placement or migration can also lead to a high block requiring intubation.\textsuperscript{27}

The incidence of intrathecal migration has been reported as 0.15–0.18%.\textsuperscript{125} \textsuperscript{142} A similar figure of 0.18% has been reported for intravenous migration.\textsuperscript{125}

\textit{Adverse events related to epidural drug administration}

\textit{Drug errors}

Most commonly, LAs, opioids and/or clonidine are infused into the epidural space to provide postoperative analgesia. All these drugs carry the potential for serious adverse effects. In addition, occasionally drug errors occur whereby the wrong drug is administered via the epidural catheter, sometimes resulting in tragic consequences. The incidence of such cases remains unclear as there are very few case reports—glucose,\textsuperscript{167} antibiotics,\textsuperscript{88} thiopentone,\textsuperscript{26} \textsuperscript{55} potassium chloride\textsuperscript{89} \textsuperscript{92} \textsuperscript{149} (resulting in paraplegia) and total parenteral nutrition\textsuperscript{120} have all been inadvertently injected.

The use of pharmacy-prepared or commercially prepared solutions, extreme care with labelling of epidural catheters and drugs, checking procedures and the use of dedicated pumps should help avoid these problems.

\textit{Respiratory depression}

The side-effect of most concern with epidural opioids is respiratory depression. Because of the hydrophilic nature of some opioids, such as morphine, there is an increased tendency for the drug to remain in the CNS, particularly the cerebrospinal fluid, resulting in possible cephalad spread and delayed respiratory depression.

There is an abundance of literature devoted to neuraxial opioids and the incidence of respiratory depression. One Swedish review, encompassing 15 departments of anaesthesia, estimated an incidence of 0.25–0.4%, the major risk factors being age over 70 yr and additional administration of opioids by other routes.\textsuperscript{64} A Canadian questionnaire, involving 56 teaching hospitals, cited an estimated incidence of 0.13%.\textsuperscript{176} Although the choice of opioid is important, fentanyl or diamorphine being more lipophilic and less likely to cause delayed respiratory depression, the dose of drug given by continuous infusion is also important. To emphasize this point, there has been a case report describing three patients who developed severe respiratory depression during an epidural infusion containing bupivacaine and fentanyl 20–25 \textmu g ml\textsuperscript{-1}.\textsuperscript{164}

The actual, not estimated, incidence of respiratory depression has been reported in numerous studies involving data collection from an APS. The number of patients studied varies between 1014 and 1 304 214, with a reported incidence of 0.24–1.6%.\textsuperscript{24} \textsuperscript{56} \textsuperscript{125} \textsuperscript{133} \textsuperscript{144} \textsuperscript{154} \textsuperscript{172} often associated with sedation.\textsuperscript{91} \textsuperscript{144} The higher figures are more representative of the incidence using epidural morphine infusion. However, with the administration of epidural morphine <200 \textmu g h\textsuperscript{-1} the risk of respiratory depression is probably no higher than with other epidural opioids.\textsuperscript{21} Using a PCEA containing fentanyl and LA, the incidence is reported as 0.3%.\textsuperscript{96}

The quoted incidence of respiratory depression when epidural analgesia is supervised by an APS is no higher than the incidence of respiratory depression seen with other forms of opioid analgesia.\textsuperscript{19} Regular monitoring of respiratory rate and, more importantly, the level of consciousness appears to be adequate to detect respiratory depression, and is indicated for up to 12 h after a bolus injection of morphine and for the entire duration of a continuous infusion.
Audit and feedback to anaesthetists, surgeons and nurses 9000 patients, the incidence of hypotension during epidural
infused at 20
Monitoring Regular monitoring of dynamic pain scores, cardiorespiratory
parameters, sedation scores, dermatomal level and motor
blockade Daily inspection of the epidural site Twice daily review by the APT
Audit Audit and feedback to anaesthetists, surgeons and nurses

Hypotension
Accompanying the sensory and motor block of epidural LAs are the sympatholytic effects due to blockade of the sympathetic chain; this results in hypotension. If the block height reaches the cardiac outflow between T1 and T5, there may be a marked hypotensive and bradycardic response, particularly in the presence of hypovolaemia. The degree of hypotension depends on the actual dose, lower concentrations of LA causing less effect on blood pressure. Unopposed parasympathetically mediated bronchoconstriction has also been proposed as the cause of a case of severe bronchospasm during epidural anaesthesia.102

Combining the results of three studies involving nearly 9000 patients, the incidence of hypotension during epidural infusion of LA is 0.7–3% depending on the concentration used (0.0625–0.25% bupivacaine) and the criteria for hypotension.45 133 159 Use of a PCEA gave a 6.8% incidence of hypotension.96

The routine use of epidural clonidine up to 900 μg as boluses of 100 μg is likely to produce significant haemodynamic depression and sedation.50 17 114 When infused at 20 μg h⁻¹ with bupivacaine and fentanyl, it was shown to improve analgesia at rest and during coughing but, again, was associated with significant haemodynamic changes.118

CNS toxicity
The incidence of CNS toxicity, notably convulsions, as a result of high plasma concentrations of free LA, was reported to be 0.01–0.12% for bupivacaine when 16 870²³ and 40 010155 epidural blocks were assessed There was a higher incidence of 0.3 per 1000 with lidocaine.23 Cerebral irritation after doses as low as 30 mg h⁻¹ has been described,49 but this is still considerably higher than the ‘optimal’ dose of bupivacaine recommended by Curatolo and colleagues for LA–opioid combination.40 A case of ropivacaine-induced seizure has been described after epidural anaesthesia.¹

Motor blockade
Excessive lower limb motor blockade with controlled infusion of epidural LAs is uncommon, occurring in only in 3.0% of cases using low concentrations of bupivacaine.¹⁴⁴ If motor blockade does occur, it may result in the development of pressure areas on the heels32 122 151 and deep venous thrombosis.¹⁶⁶ Persistent motor blockade of one or both lower limbs in a patient receiving a low dose combination LA–opioid thoracic epidural should always be treated with suspicion. Stopping the epidural infusion normally results in neurological improvement within 2 h. If this does not occur, consideration should be given to excluding a spinal haematoma or abscess. Ropivacaine may produce less motor blockade compared with an equianalgesic dose of bupivacaine,¹⁷⁴ especially if used in low concentrations (0.1%) with fentanyl (2 μg ml⁻¹).96 Epidural blockade has been blamed in occasional case reports for masking the symptoms of compartment syndrome,¹¹² 153 156 although there have also been cases which have been diagnosed successfully during epidural blockade.¹² ¹¹¹

Organizational issues
Providing effective analgesia for patients undergoing major surgery is a daily challenge for most clinical anaesthetists. Continuous thoracic epidural analgesia with a low-dose LA–opioid combination has the potential to provide effective dynamic pain relief for many patients, even those undergoing major upper abdominal or thoracic procedures. This level of pain relief is central to early mobilization and rapid rehabilitation. However, in the hurly-burly of a busy surgical ward, it is not uncommon for epidurals to be ineffective in terms of providing dynamic pain relief. Rarely, and catastrophically, major damage to the patient may occur.

The major factors to be considered in the safe and effective management of ward-based epidural analgesia are shown in Table 6.

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