Indications and contraindications for thoracic epidural analgesia in multiply injured patients

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KEYWORDS
Rib fractures; Epidural analgesia; Pain control

Summary
Background and objectives: Rib fractures are associated with significant morbidity and mortality. Previous studies have demonstrated a significant reduction in pneumonia and duration of mechanical ventilation with epidural analgesia (EA) following multiple rib fractures. There remains controversy regarding the appropriate indications and contraindications for EA in multiply injured patients. We sought to determine the factors underlying the decision to use or not to use EA in these patients.

Methods: A survey was sent to the directors of pain management services at all American College of Surgeons Committee on Trauma (ACS-COT) designated Level I trauma centers in the U.S. The survey queried their opinion regarding the appropriateness of 33 contraindications and eight indications for EA after rib fractures.

Results: The response rate was 43% (81/188). Ninety-five percent of responding centers indicated that EA is used after rib fractures, but only 15% had guidelines defining the indications and contraindications. There was general agreement (>80%) regarding the indications for EA but disagreement regarding the contraindications. Contraindications were categorised based on the degree of agreement of respondents. The areas of greatest controversy involved minor spine injuries and minor coagulopathy.

Conclusions: There is wide variability regarding contraindications employed for thoracic epidural analgesia following rib fractures. These data support the need for evidenced based guidelines to define the use of EA in the multiply injured patient.

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1. Introduction

Rib fractures have been associated with significant morbidity and mortality following traumatic injury. The presence of three or more rib fractures has been associated with increased mortality and duration of ICU and hospital care [1,2]. A recent analysis of the National Trauma Databank demonstrated a significant increase in mortality and pulmonary morbidity for each additional rib fracture [3]. The elderly are particularly susceptible to complications of rib fractures with nosocomial pneumonia rates reported as high as 31% [4]. The pain associated with rib fractures leads to impaired ventilatory function and thus increases pulmonary morbidity. Management of these patients is therefore focused on achieving adequate analgesia and clearance of pulmonary secretions. Previous studies have demonstrated that epidural analgesia provides superior pain relief, improved pulmonary function tests, reduced the risk of developing nosocomial pneumonia and led to a shorter duration of mechanical ventilation compared to intravenous opioids [5–9]. Despite these advantages only 2% of patients with rib fractures in the National Trauma Databank received epidural analgesia [3]. This may be due in large part to controversy regarding the indications and contraindications for the use of epidural analgesia in patients with multiple injuries. We sought to define the current practice in the United States by surveying pain service directors at Level 1 trauma centers regarding their current guidelines for the use of epidural analgesia in this patient population and to assess the level of agreement regarding indications and contraindications for its use.

2. Methods

A list of all Level 1 trauma centers in the United States was obtained from the American College of Surgeons Committee on Trauma. A written survey was sent to the pain service directors at all centers in September of 2004. Respondents were asked whether epidural analgesia was used for the management of pain following rib fractures and if so were there established institutional guidelines regarding the use of epidural analgesia in patients with multiple injuries. We sought to define the current practice in the United States by surveying pain service directors at Level 1 trauma centers regarding their current guidelines for the use of epidural analgesia in this patient population and to assess the level of agreement regarding indications and contraindications for its use. To develop a rank listing of contraindications, answers A and C were pooled as general agreement that a contraindication was appropriate and the percent of respondents in this category was listed in descending order. Indications were ranked as either appropriate or inappropriate. The indications and contraindications included were based on our recent experience with a randomised controlled trial of epidural analgesia in this patient population [5]. Respondents were not asked to suggest additional indications or contraindications but were asked to send their institutional guideline if available. Review of these did not reveal any additional factors. Three mailings of the survey were sent to non-responders in an effort to improve the response rate, telephone calls to non-respondents were not permitted.

3. Results

Responses were received from 81/188 (43%) of US Level 1 trauma centers. Seventy-seven of the centers indicated that epidural analgesia is used at their institution for management of pain after rib fractures (95%). Twelve centers (15%) reported that they had developed institutional guidelines regarding the indications and contraindications for the use of epidural analgesia in this patient population. As illustrated in Table 1, there was general agreement regarding the indications for the use of EA

| Table 1 Rank list based on % of respondents supporting each indication |
|---------------------------------|------------------|
| Indication                        | Support (%)    |
| Inadequate pain control with systemic analgesics | 98              |
| Patient sedated by systemic analgesics | 95              |
| ≥ 3 rib fractures | 83              |
| Request from physician team providing primary post trauma care | 83              |
| IRB approved research study of effectiveness of epidural analgesia for pain relief | 81              |
| Request from nurses providing primary post trauma care | 43              |
| Demand from physician team providing primary post trauma care | 36              |
Table 2  Rank list based on % of respondents supporting each contraindication

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Support (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;50 k</td>
<td>93</td>
</tr>
<tr>
<td>Cellulitis at insertion site</td>
<td>92</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>90</td>
</tr>
<tr>
<td>Epidural or spinal cord haematoma</td>
<td>90</td>
</tr>
<tr>
<td>INR &gt; 1.5</td>
<td>90</td>
</tr>
<tr>
<td>LMW heparin w/in 8 h</td>
<td>88</td>
</tr>
<tr>
<td>Major TBI (GCS &lt; 8)</td>
<td>83</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>81</td>
</tr>
<tr>
<td>Penetrating head injury</td>
<td>77</td>
</tr>
<tr>
<td>Haemodynamic instability</td>
<td>74</td>
</tr>
<tr>
<td>Unable to obtain consent</td>
<td>69</td>
</tr>
<tr>
<td>LMW heparin w/in 12 h</td>
<td>69</td>
</tr>
<tr>
<td>Full spine precautions</td>
<td>68</td>
</tr>
<tr>
<td>Platelet count &lt;80 k</td>
<td>65</td>
</tr>
<tr>
<td>TBI (GCS 8—13)</td>
<td>64</td>
</tr>
<tr>
<td>Patient deeply sedated for vent</td>
<td>63</td>
</tr>
<tr>
<td>Injury to thoracic aorta</td>
<td>62</td>
</tr>
<tr>
<td>Ligament disruption thoracic spine</td>
<td>62</td>
</tr>
<tr>
<td>Ligament disruption cervical spine</td>
<td>57</td>
</tr>
<tr>
<td>Ligament disruption lumbar spine</td>
<td>52</td>
</tr>
<tr>
<td>Unstable pelvic fracture</td>
<td>47</td>
</tr>
<tr>
<td>Normal thoracic spine films, unable to examine</td>
<td>43</td>
</tr>
<tr>
<td>Transverse process fracture, thoracic spine</td>
<td>43</td>
</tr>
<tr>
<td>Spinous process fracture, thoracic spine</td>
<td>40</td>
</tr>
<tr>
<td>Normal lumbar spine films, unable to examine</td>
<td>40</td>
</tr>
<tr>
<td>Transverse process fracture, cervical spine</td>
<td>38</td>
</tr>
<tr>
<td>Spinous process fracture, cervical spine</td>
<td>37</td>
</tr>
<tr>
<td>Normal cervical spine films, unable to examine</td>
<td>35</td>
</tr>
<tr>
<td>Respiratory failure w/o impaired mechanics</td>
<td>35</td>
</tr>
<tr>
<td>Spinous process fracture, lumbar spine</td>
<td>30</td>
</tr>
<tr>
<td>Transverse process fracture, lumbar spine</td>
<td>29</td>
</tr>
<tr>
<td>1.0 &lt; INR &lt; 1.5</td>
<td>24</td>
</tr>
<tr>
<td>&lt;3 rib fractures</td>
<td>18</td>
</tr>
</tbody>
</table>

in this setting (Table 1). Of the 33 contraindications evaluated, they were grouped based on the general level of agreement as shown in Table 2. In addition, specific survey results are presented for complications grouped by common classification.

3.1. Contraindications related to coagulopathy

As shown in Fig. 1, there were six contraindications that addressed the issue of coagulopathy in trauma patients. The majority of respondents felt that a platelet count <50,000, INR > 1.5, or administration of low molecular weight heparin (LMWH) within the previous 8 h were appropriate contraindications to placement of a thoracic epidural catheter. Opinions were mixed regarding a platelet count <80,000 or administration of LMWH within the previous 12 h. The majority of respondents did not believe that INR between 1.0 and 1.5 was an appropriate contraindication.

3.2. Contraindications related to spinal evaluation

As many trauma patients admitted to the intensive care unit are still undergoing evaluation for potential spinal injury, we inquired whether the spine clearance status was an appropriate contraindication to thoracic epidural placement. We included as contraindications an admission status of full spine precautions and a series of questions regarding normal imaging at different spine levels but the inability to evaluate the patient clinically for pain that may be associated with ligamentous injury. As illustrated in Fig. 2, the majority of respondents felt that full spine precaution status was an appropriate contraindication, but there was disagreement among the other categories with most reporting these as inappropriate or relative but rarely applied contraindications to epidural catheter placement.

3.3. Contraindications related to spine injury

As illustrated in Fig. 3, we defined a series of contraindications based on the degree of documented spinal injury at the cervical, thoracic, and lumbar spine levels. The majority of respondents agreed that documented spinal cord injury or known spinal or epidural haematomas were appropriate contraindications. However, there was wide variability in the opinions regarding more minor spinal injuries including ligamentous disruption and transverse or spinous process fractures.

3.4. Contraindications related to associated injuries

As the majority of blunt traumatic injuries leading to rib fractures result from motor vehicle collisions, associated injuries are common and may impact the decision to place a thoracic epidural catheter. Fig. 4 illustrates the responses to contraindications listed in this area. The majority of
Fig. 1 Contraindications related to coagulopathy. The distribution of responses regarding the appropriateness of contraindications to thoracic epidural placement relative to patient coagulopathy is illustrated. Response categories include: appropriate contraindication, relative contraindication commonly applied, relative contraindication uncommonly applied, inappropriate contraindication, and no response. Abbreviations: INR, international ratio; LMW, low molecular weight.

Respondents agreed that significant traumatic brain injury and haemodynamic instability were appropriate contraindications. There was less agreement regarding unstable pelvic fracture, injury to the thoracic aorta and the need for deep sedation for ventilator support.

4. Discussion

The use of epidural analgesia in the multiply injured patient with rib fractures is limited by several potential contraindications to the placement of an epidural catheter. The risks of catheter
Fig. 3  Contraindications related to spine injury. The distribution of responses regarding the appropriateness of contraindications to thoracic epidural placement relative to spine injury is illustrated. Response categories include: appropriate contraindication, relative contraindication commonly applied, relative contraindication uncommonly applied, inappropriate contraindication, and no response. Abbreviations: C, cervical; T, thoracic; L, lumbar; fx, fracture.

Fig. 4  Contraindications related to associated injuries. The distribution of responses regarding the appropriateness of contraindications to thoracic epidural placement relative to associated injuries is illustrated. Response categories include: appropriate contraindication, relative contraindication commonly applied, relative contraindication uncommonly applied, inappropriate contraindication, and no response. Abbreviations: TBI, traumatic brain injury; GCS, Glasgow coma score; vent, ventilator.
with altered mental status and thus patients with associated traumatic brain injury are often excluded. Finally, a high proportion of patients with rib fractures as a result of high-energy blunt trauma have associated spine injuries that may interfere with placement of the catheter or raise concern regarding the development of neurologic sequelae. In our previous randomised controlled trial of epidural analgesia vs. intravenous opioids we found that 69% of eligible patients met an exclusion criteria due to contraindications to placement of the epidural catheter that had been established for study purposes. The vast majority of these were due to minor associated spine injuries. This survey was conducted to determine the current consensus among pain service directors at Level 1 trauma centers in the United States regarding the indications and contraindications for epidural catheter placement in these patients.

This report demonstrates general agreement regarding the common indications for thoracic epidural placement but significant disagreement regarding a number of the contraindications listed.

Guideline for Assessment & Management of Patients with Multiple Rib Fractures

Patient admitted with

1. Notify Respiratory therapy for frequent assessment and broncho-pulmonary hygiene
2. Initial pain control: IV opioids, PCA for alert patients, intermittent pm for patients with altered mental status
3. Consider NSAID if no contraindication
4. Acute Pain Relief Service (APS) consultation w/in 12 hours to consider epidural analgesia

Absolute Contraindications
- Injury pattern: spinal cord injury, epidural or spinal cord hematoma, thoracic vertebral body fracture
- Active coagulopathy: platelet count < 50K, INR > 1.5
- Infection: cellulitis at insertion site, bacteremia with septic shock

Relative Contraindications
- Inability to position patient due to associated injury
- Platelet count 50-100,000
- Severe Traumatic Brain Injury requiring ICP monitoring
- Incomplete evaluation for spine fracture
- Low Molecular Weight heparin dose w/in last 12 hrs*

Contraindications are reassessed as patient condition improves, *epidural placement delayed until > 12 hours from last LMW Heparin dose

Obtain consent and place catheter
Start analgesic infusion
All pain issues managed by APS until conversion to oral medications

YES
Epidural candidate?
No
Continue intravenous opioids
+/- NSAIDS
All pain issues managed by APS
Until conversion to oral medications

Note: Acute Pain Relief Service is a service staffed by anesthesiologists and mid-level practitioners specializing in pain management and available 24/7 for consultation and complex pain management

Fig. 5 Local guideline for assessment and management of patients with multiple rib fractures.
A similar survey was recently reported regarding the use of thoracic epidural analgesia in the United Kingdom [13]. While this study did not focus on its use in multiply injured patients, it did report little consensus regarding the degree of coagulopathy that would be tolerated prior to catheter placement. This included controversy regarding the timing of catheter placement relative to a prophylactic dose of LMWH and disagreement over the appropriate INR and platelet count for catheter placement. A subsequent survey evaluated the use of epidural analgesia in an intensive care setting in England [14]. In this survey, the presence of subclinical coagulopathy was considered a contraindication to epidural placement by only 49% of the intensive care units surveyed. A consensus document has been recently produced regarding the use of regional anesthesia in anticoagulated patients, but this does not specifically address patients with coagulopathy following injury [11]. These reports coupled with our data highlight the current lack of consensus regarding the appropriate contraindications for epidural catheter placement among the critically ill or injured.

It is our hope that this survey will stimulate the specialty societies to develop an evidence-based consensus guideline for the use of thoracic epidural analgesia for management of pain following rib fracture in the multiply injured patient. We have developed a local guideline for the providers in our trauma center that is provided as Fig. 5, but recognise that this has not been subject to a national consensus process. As shown, we consider all patients with \( \geq 3 \) rib fractures as candidates for evaluation by our Acute Pain Relief Service (APS). This service consists of anesthesiologist and mid-level practitioners specialising in the management of acute pain and available 24/7 for consultation and complex pain management. Patients are considered for ICU admission if they have any respiratory compromise, significant pulmonary morbidity or are \( \geq 65 \) years of age. All patients receive respiratory therapy and initial pain management with intravenous opioids pending assessment for epidural analgesia. Our absolute and relative contraindications are noted in Fig. 5. Importantly, all patients with multiple rib fractures have their pain managed by APS regardless of whether they are candidates for epidural analgesia.

The primary limitation to this survey is the response rate of 43%. There may be a selection bias introduced by those who chose to respond to our survey. Despite three mailings of the survey to non-responders, we were unable to improve this response rate. The survey only included Level 1 trauma centers and thus may not be representative of the practice in the general community. Level 1 centers, however, generally treat the greatest number of severely injured patients and thus the fact that only 15% of respondents reported the existence of guidelines regarding the use of epidural analgesia in multiply injured patients suggests that this has not been widely recognised as a practice issue. We believe that our data point to the need for the development of evidence based guidelines for the use of thoracic epidural analgesia for the management of patients with rib fractures in the setting of multiple injuries.

Conflict of interest statement

There is no conflict of interest.

References


A comparison of regional and general anaesthesia for total replacement of the hip or knee

A META-ANALYSIS

S. Hu, Z.-Y. Zhang, Y.-Q. Hua, J. Li, Z.-D. Cai
From the Second Military Medical University, Shanghai, People’s Republic of China

We performed a meta-analysis to evaluate the relative efficacy of regional and general anaesthesia in patients undergoing total hip or knee replacement. A comprehensive search for relevant studies was performed in PubMed (1966 to April 2008), EMBASE (1969 to April 2008) and the Cochrane Library. Only randomised studies comparing regional and general anaesthesia for total hip or knee replacement were included.

We identified 21 independent, randomised clinical trials. A random-effects model was used to calculate all effect sizes. Pooled results from these trials showed that regional anaesthesia reduces the operating time (odds ratio (OR) -0.19; 95% confidence interval (CI) -0.33 to -0.05), the need for transfusion (OR 0.45; 95% CI 0.22 to 0.94) and the incidence of thromboembolic disease (deep-vein thrombosis OR 0.45, 95% CI 0.24 to 0.84; pulmonary embolism OR 0.46, 95% CI 0.29 to 0.80).

Regional anaesthesia therefore seems to improve the outcome of patients undergoing total hip or knee replacement.

In 2005, more than 375,000 patients underwent total hip replacement (THR) and more than 530,000 had total knee replacement (TKR) in the United States. Despite the frequency with which these procedures are carried out, there remains controversy as to whether they are best performed under regional anaesthesia using epidural or spinal neuraxial blockade, or general anaesthesia. In 2000, Rodgers et al published a meta-analysis which addressed the clinical merits of neuraxial blockade for a variety of surgical procedures. However, its place in patients undergoing joint replacement remains uncertain.

Regional anaesthesia in total joint replacement is claimed to decrease the incidence of deep-vein thrombosis (DVT) and pulmonary embolism and to reduce intraoperative bleeding, the need for transfusion and the length of hospital stay. It can also increase patient satisfaction especially after one-stage bilateral THR or TKR. Epidural anaesthesia combined with post-operative epidural analgesia can reduce the physiological stress of surgery and the incidence of complications as well as improving the overall outcome of surgery. However, other studies have reported contradictory results. Moiniche et al have shown that there may not be any advantage in regional techniques. Moreover, spinal and epidural anaesthesia and analgesia may cause hypotension, motor blockade, urinary retention and pruritus. Although there have been many refinements to reduce such complications, there is still the potential for inadvertent dural puncture and neurological injury which may make these techniques less acceptable. In addition, many of these studies have been compromised by small numbers of patients and, in some cases, the relatively rare occurrence of complications. Consequently, it has been difficult to draw any conclusions about the effect of the choice of anaesthesia on the outcome of joint replacement.

We carried out a meta-analysis to evaluate the relative efficacy of regional and general anaesthesia in patients undergoing joint replacement. We concentrated on THR and TKR and restricted the regional techniques to epidural or spinal approaches, to limit the number of confounding variables.

Materials and Methods
A search of the literature was undertaken using PubMed (1966 to April 2008), EMBASE (1969 to April 2008) and the Cochrane Library databases using the following keywords: hip replacement, hip arthroplasty, knee replacement, knee arthroplasty, regional anaesthesia, epidural anaesthesia, spinal anaesthesia and general anaesthesia. The terms regional, epidural, spinal and general anaesthesia were
linked with ‘or’ and combined using ‘and’ with each subsequent term. Each publication was independently reviewed by two authors (SH, Z-DC) and the data collected entered onto a standard sheet. We limited the search to articles published in English. Only randomised, controlled trials which compared the outcome of elective THR and TKR carried out under regional anaesthesia with those carried out under general anaesthesia were included. We included all of these despite the fact that some did not address all the aspects that we wished to study. Nonetheless, we read all the original articles carefully and extracted relevant data in order to decrease publication bias. We also checked the references of each article for other studies which met all our inclusion criteria. We extracted the following outcome data from each article for other studies which met all our inclusion criteria — the operating time, the intraoperative blood loss, the number of patients requiring blood transfusion, the number of patients with DVT or pulmonary embolism, diagnosed radiologically or clinically, the length of hospital stay and any deaths.

The data collection was not blinded. A third reviewer (Z-YZ) compared the two sets of data collection sheets and any differences were resolved by discussion and reconfirming the data from the original paper. We attempted to contact the authors of a trial if they had published more than one report on the subject to confirm that the data in each of their publications were from different groups of patients. Lastly, we asked authors if they knew of any other relevant published studies.

**Statistical analysis.** We only included those outcome parameters which were presented in numerical format. Continuous outcome parameters were expressed as the mean and SD and dichotomous outcomes as the number of events. The level of significance for all tests was set at a two-sided p-value of 0.05 and variances were not assumed to be equal. Patients who had a general anaesthetic were treated as a control group, and those with regional anaesthesia as an intervention group. The odds ratios (OR) and the 95% confidence interval (CI) were calculated for dichotomous outcomes. The standardised mean difference and the 95% CI were presented for continuous outcomes. Heterogeneity among studies was tested using the chi-squared test. We used a random-effects model to calculate all effect sizes since it was more conservative and included both the random variation within the studies and the variation among the different studies. Moreover, the pooled estimates calculated by the random-effects and fixed-effects models were similar when there was minimal heterogeneity between studies. Whenever possible, subgroup analyses were performed to detect and evaluate clinically significant differences. All statistical analyses were performed using the freeware program Review Manager 4.2 (Cochrane Collaboration, Oxford, United Kingdom).

### Table I. Characteristics of the randomised controlled trials of regional versus general anaesthesia in total joint replacement of the lower limb contributing data to our meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Joint studied*</th>
<th>Regional anaesthesia technique</th>
<th>Outcomes studied†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modig et al²</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, DVT, PE</td>
</tr>
<tr>
<td>Modig et al³</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, DVT, PE</td>
</tr>
<tr>
<td>Modig et al⁴</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, DVT, PE</td>
</tr>
<tr>
<td>Davis et al⁵</td>
<td>THR</td>
<td>Spinal</td>
<td>Duration of surgery, blood loss, number of patients transfused, DVT, PE</td>
</tr>
<tr>
<td>Jørgensen et al⁶</td>
<td>TKR</td>
<td>Continuous epidural</td>
<td>DVT, PE</td>
</tr>
<tr>
<td>Nielsen et al⁷</td>
<td>TKR</td>
<td>Continuous epidural</td>
<td>DVT</td>
</tr>
<tr>
<td>Brueckner et al¹²</td>
<td>THR</td>
<td>Spinal</td>
<td>Duration of surgery, blood loss</td>
</tr>
<tr>
<td>Planes et al¹³</td>
<td>THR</td>
<td>Spinal</td>
<td>Duration of surgery, blood loss, DVT</td>
</tr>
<tr>
<td>Mitchell et al¹⁴</td>
<td>TKR</td>
<td>Continuous epidural</td>
<td>DVT</td>
</tr>
<tr>
<td>Borghi et al¹⁷</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, number of patients transfused</td>
</tr>
<tr>
<td>Gonano et al²⁴</td>
<td>THR or TKR</td>
<td>Spinal</td>
<td>Duration of surgery</td>
</tr>
<tr>
<td>Lattermann et al²⁵</td>
<td>THR</td>
<td>Combined spinal and epidural</td>
<td>Duration of surgery, blood loss</td>
</tr>
<tr>
<td>Kita et al²⁶</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, length of hospital stay</td>
</tr>
<tr>
<td>Kudoh et al²⁷</td>
<td>TKR</td>
<td>Spinal</td>
<td>Duration of surgery, blood loss, PONV</td>
</tr>
<tr>
<td>Modig and Karlstrom²⁸</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss</td>
</tr>
<tr>
<td>Wulf et al²⁹</td>
<td>THR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, length of hospital stay</td>
</tr>
<tr>
<td>Donatelli et al³⁰</td>
<td>THR or TKR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, number of patients transfused</td>
</tr>
<tr>
<td>Hole et al³¹</td>
<td>THR</td>
<td>Single-injection epidural</td>
<td>Duration of surgery, PE</td>
</tr>
<tr>
<td>Jones et al³²</td>
<td>THR or TKR</td>
<td>Spinal</td>
<td>Duration of surgery, number of patients transfused, length of hospital stay, DVT, PE mortality</td>
</tr>
<tr>
<td>Williams-Russo et al³³</td>
<td>TKR</td>
<td>Continuous epidural</td>
<td>Duration of surgery, blood loss, DVT, PE</td>
</tr>
<tr>
<td>Keith³⁴</td>
<td>THR</td>
<td>Single-injection epidural</td>
<td>Blood loss, number of patients transfused</td>
</tr>
</tbody>
</table>

* THR, total hip replacement; TKR, total knee replacement
† DVT, deep-vein thrombosis; PE, pulmonary embolism; PONV, post-operative nausea and vomiting
‡ the data of the two publications of Davis et al (6, 20) were from the same group as were those presented by Borghi et al (21,22) in their two publications
Results

We identified 25 randomised, controlled trials in the English language in which patients had been randomised to receive either regional or general anaesthesia. Of these, one in which the data were reported as medians and ranges was excluded. Ab Another three were also excluded. One did not present data in a form which could be included in the review and the other two included confounding factors, namely peri-operative hypotension and hip trauma. Two studies generated more than one publication each, but were counted only once. Finally, 21 studies were included in the review (Table I). We assessed the presence of publication bias by examining funnel plots which displayed the studies included in the meta-analysis in a plot of effect size against sample size. Fortunately, they showed no evidence of publication bias for the operating time, intraoperative bleeding, rate of transfusion, and the incidence of DVT and pulmonary embolism.

Whenever possible, we also performed several subgroup analyses on the hips and knees independently and then combined them to provide an overall estimate. The results of the meta-analysis are shown in Tables II and III.

Table II. Results of the meta-analysis for all the outcomes of total joint replacement

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>SMD or OR (95% CI)</th>
<th>Z-value</th>
<th>p-value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi-squared test</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>17</td>
<td>SMD -0.12 (-0.23 to -0.02)</td>
<td>2.36</td>
<td>0.02</td>
<td>13.99</td>
</tr>
<tr>
<td>Intra-operative blood loss</td>
<td>12</td>
<td>SMD -0.50 (-0.96 to -0.04)</td>
<td>2.12</td>
<td>0.03</td>
<td>107.04</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>3</td>
<td>SMD -0.55 (-2.47 to +1.37)</td>
<td>0.57</td>
<td>0.57</td>
<td>4.31</td>
</tr>
<tr>
<td>Number of transfusions</td>
<td>5</td>
<td>OR 0.45 (0.22 to 0.94)</td>
<td>2.14</td>
<td>0.03</td>
<td>8.94</td>
</tr>
<tr>
<td>DVT</td>
<td>10</td>
<td>OR 0.45 (0.24 to 0.84)</td>
<td>2.48</td>
<td>0.01</td>
<td>28.88</td>
</tr>
<tr>
<td>PE</td>
<td>8</td>
<td>OR 0.46 (0.21 to 1.02)</td>
<td>1.9</td>
<td>0.06</td>
<td>11.85</td>
</tr>
<tr>
<td>PONV</td>
<td>2</td>
<td>OR 0.27 (0.11 to 0.64)</td>
<td>2.96</td>
<td>0.003</td>
<td>0.19</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>OR 0.94 (0.14 to 6.52)</td>
<td>0.06</td>
<td>0.95</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* DVT, deep-vein thrombosis; PE, pulmonary embolism; PONV, post-operative nausea and vomiting
† SMD, standardised mean difference; OR, odds ratio; 95% CI, 95% confidence interval
‡ inconsistency value, this represents the extent of the heterogeneity

Table III. Subgroup analysis of some of the outcome assessments

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup†</th>
<th>Number of studies</th>
<th>SMD or OR (95% CI)‡</th>
<th>Z-value</th>
<th>p-value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi-squared test</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>THR</td>
<td>12</td>
<td>SMD -0.19 (-0.33 to -0.05)</td>
<td>2.69</td>
<td>0.007</td>
<td>9.57</td>
</tr>
<tr>
<td></td>
<td>TKR</td>
<td>2</td>
<td>SMD -0.02 (-0.21 to +0.17)</td>
<td>0.21</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Intra-operative blood loss</td>
<td>THR</td>
<td>10</td>
<td>SMD -0.65 (-1.24 to -0.06)</td>
<td>2.16</td>
<td>0.03</td>
<td>103.24</td>
</tr>
<tr>
<td></td>
<td>THR¶</td>
<td>8</td>
<td>SMD -0.48 (-1.13 to 0.17)</td>
<td>1.44</td>
<td>0.15</td>
<td>82.8</td>
</tr>
<tr>
<td>Number of transfusions</td>
<td>THR</td>
<td>4</td>
<td>OR 0.35 (0.18 to 0.67)</td>
<td>3.19</td>
<td>0.001</td>
<td>4.16</td>
</tr>
<tr>
<td></td>
<td>TKR</td>
<td>None</td>
<td>OR 0.35 (0.18 to 0.67)</td>
<td>3.19</td>
<td>0.001</td>
<td>4.16</td>
</tr>
<tr>
<td>DVT</td>
<td>No TED drug prophylaxis</td>
<td>7</td>
<td>OR 0.27 (0.14 to 0.52)</td>
<td>3.88</td>
<td>0.0001</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>TED drug prophylaxis</td>
<td>3</td>
<td>OR 1.07 (0.58 to 1.97)</td>
<td>0.21</td>
<td>0.83</td>
<td>2.78</td>
</tr>
<tr>
<td>PE</td>
<td>No TED drug prophylaxis</td>
<td>6</td>
<td>OR 0.26 (0.13 to 0.52)</td>
<td>3.87</td>
<td>0.0001</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>TED drug prophylaxis</td>
<td>2</td>
<td>OR 1.66 (0.61 to 4.52)</td>
<td>1.0</td>
<td>0.32</td>
<td>0.70</td>
</tr>
</tbody>
</table>

* DVT, deep-vein thrombosis; PE, pulmonary embolism
† THR, total hip replacement; TKR, total knee replacement; TED, thromboembolic disease
‡ SMD, standardised mean difference; OR, odds ratio; 95% CI, 95% confidence interval
§ inconsistency value, this represents the extent of the heterogeneity
¶ two trials in which patients in the regional anaesthesia group had a lower blood pressure than those in the general anaesthesia group were excluded
Intra-operative blood loss. Intraoperative blood loss was reported in 12 studies which included 880 patients. In five there was no statistical difference in the intraoperative blood loss between regional and general anaesthesia. In another five there was reduced blood loss with regional anaesthesia. The remaining two showed increased blood loss. These differences were statistically significant (standardised mean difference -0.50, 95% CI -0.96 to -0.04; Table II).

The pooled data from the ten studies on THR showed a statistically significant decrease in blood loss in patients with regional anaesthesia (standardised mean difference -0.65; 95% CI -1.24 to -0.06; Table III). However, when we excluded two trials in which patients in the regional anaesthesia group had a significantly lower blood pressure than those in the general anaesthesia group, there was no significant difference between the groups (Fig. 2).

Transfusion requirement. Five studies included data on the number of patients transfused intraoperatively. Meta-analysis showed that regional anaesthesia reduced the need for transfusion (OR 0.45; 95% CI 0.22 to 0.94; Table II). Subset modelling of the THR group showed that regional anaesthesia reduced the need for transfusion (OR 0.35; 95% CI 0.18 to 0.67; Table III). None of the studies presented comparable data for the TKR group and...
therefore the effect of regional anaesthesia on the need for transfusion in TKR could not be determined.

**Thromboembolic disease.** Ten studies presented data on the incidence of DVT \(3-6,8,9,13,14,32,33\) and eight on pulmonary embolism. \(3-6,8,31-33\) These two meta-analyses showed that regional anaesthesia significantly lowered the incidence of thromboembolic disease when compared with general anaesthesia (DVT 95% CI 0.24 to 0.84; Fig. 3). Although a random-effects model did not show the difference (pulmonary embolism 95% CI 0.21 to 1.02; Table II), it was identified using a fixed-effects model (pulmonary embolism 95% CI 0.29 to 0.80; Fig. 4).

However, when subgroup analysis was performed of the studies in which patients had been given anticoagulants, \(13,14,31,33\) there was no significant difference in the incidence of thromboembolic disease between the two groups (DVT 95% CI 0.58 to 1.97; Fig. 3; pulmonary embolism 95% CI 0.61 to 4.52; Table III).

**Post-operative nausea and vomiting.** Data on the number of patients who suffered from this were only given in two studies \(24,27\) (OR 0.27; 95% CI 0.11 to 0.64; Table II). One noted that regional anaesthesia reduced its incidence, \(17\) but pooled data showed significant difference between the two groups.

**Other outcome measurements.** Data on mortality were presented in only two studies \(13,32\) (OR 0.94; 95% CI 0.14 to 6.52; Table II). There was no obvious difference between regional and general anaesthesia. Meta-analysis was not performed because of insufficient data.

Three studies recorded the length of hospital stay. \(29,32,33\) There was no discernible difference between the groups (standardised mean difference -0.55; 95% CI -2.47 to +1.37; Table II).

**Discussion**

Our meta-analysis has shown several potential advantages of regional over general anaesthesia. The former can be beneficial in reducing the duration of surgery, the need for transfusion, post-operative nausea and vomiting and the incidence of thromboembolic disease (DVT and pulmonary embolism) in patients undergoing total joint replacement, particularly THR. There was insufficient evidence to support or refute the use of regional anaesthesia in decreasing intra-operative blood loss, mortality or length of hospital stay.

Duration of surgery refers to the operating time and not to the duration of anaesthesia or recovery. Our meta-analysis has shown that regional anaesthesia had only a minimal effect in reducing the operating time. Sub-group
analysis indicated that regional anaesthesia significantly reduced the operating time for THR, a result which was consistent with that of other recent studies. However, this effect was not seen in patients undergoing TKR. The difference may relate to the use of a thigh tourniquet during TKR. The tourniquet gives an almost bloodless operating field which, in turn, may speed up the operation.

The pooled data showed a statistically significant decrease in blood loss in the regional anaesthesia group. However, some of the studies were performed 20 years ago and patients in the regional anaesthesia groups had a significantly lower blood pressure. A subgroup analysis of the eight THR studies, showed that there was no significant difference between the groups when this confounding factor was excluded. This is at odds with recent research by Mauermann et al. The explanation for this discrepancy may be that the latter included studies in which patients in the regional anaesthesia group had significant perioperative hypotension. Therefore we think the result from our subgroup analysis is more appropriate and conclusive. In the only study for which valid data about intra-operative blood loss was available there was no significant difference between the two groups. They did not present the data in a form which could be included in the meta-analysis. Several other studies did not find any discernible difference between the two groups. This is easily explained. Bleeding after TKR, which is performed under tourniquet, occurs after the period of the anaesthetic effect, into surgical drains. Although we cannot refute the possibility that regional anaesthesia reduces blood loss in TKR, we contend that, if there is such an effect, it is probably very small. Data on the need for transfusion were reported in five studies. We found that the use of regional anaesthesia reduced the risk of blood transfusion. The overall blood loss was not significantly different between the two methods of anaesthesia, but significant differences were found between the groups as to the need for transfusion. We believe that the reason for this may be that patients having regional anaesthesia for a THR are given a plasma expander more often than those who have general anaesthesia. Consequently, while general anaesthesia for THR would appear to increase the need for blood transfusion, patients who have regional anaesthesia either for THR or TKR require significantly greater amounts of colloid to maintain their intravascular volume in order to compensate for sympathetic vasodilatation, thereby apparently reducing the need for blood transfusions.

The prevention of thromboembolic disease is of concern to all orthopaedic surgeons. Our meta-analysis showed a protective effect of regional anaesthesia against thromboembolic disease (DVT and pulmonary embolism) in patients undergoing total joint replacement. A similar effect has been demonstrated by others. This finding was also consistent with the results published by Rodgers et al which included over 9500 patients. There are many possible reasons for this effect including altered coagulability, increased volume flow to the lower limbs, an improved ability to breathe without pain and a reduction in the surgical stress responses. However, most of the studies which favour regional anaesthesia were carried out on patients who did not have heparin prophylaxis. These findings must be viewed cautiously. A previous review showed that regional anaesthesia was inadequate as sole prophylaxis, although it may reduce the incidence of thromboembolic disease by 50%. However, a recent review showed that epidural anaesthesia without anticoagulants resulted in a low incidence of venous thromboembolism in patients undergoing THR. We suggest that on this basis regional anaesthesia, when used in conjunction with a prophylactic anticoagulant, will be more beneficial in decreasing the rate of thromboembolism, especially in those patients with risk factors such as varicose veins.
malignancy and smoking. old age and the use of oral oestrogens.6

Our data have shown that the incidence of post-operative nausea and vomiting was significantly lower in the regional group than in the general anaesthesia group. Some authors have suggested that this is because regional anaesthesia provides significantly better post-operative analgesia,41 which leads to a lower consumption of opioids. However, the sample size was small and the impact of regional anaesthesia on post-operative nausea and vomiting was inconclusive.

In our meta-analysis, we failed to confirm that regional anaesthesia was associated with a reduced length of stay in hospital or reduced mortality.

Despite the relatively large number of patients studied, there were several limitations to our study. First, we limited our meta-analysis to articles in English. Although the effect of excluding non-English trials on the results of a meta-analysis is unclear, exclusion of such trials may have little effect on the summary effects of treatment and may actually give a more conservative estimate of the effect of treatment.42 Secondly, although the data were weighted by trial size, they were not weighted by the quality of the randomised controlled trials included nor were they assessed in a blinded fashion. We believe that the quality of the trials was generally similar, since all were randomised and controlled. We also used a random-effects model for meta-analysis, which assumed some heterogeneity between studies and was thus more stringent in assigning statistical significance than a fixed-effect model. Lastly, although these data represent most of the randomised evidence available, the CIs were wide for many outcomes and the summary estimates of effect (OR and standardised mean difference) should be interpreted with caution.

In conclusion, our data support the recent trend towards the increased use of regional anaesthesia. Furthermore, epidural anaesthesia/analgesia has been shown to improve the post-operative outcomes by relieving pain, reducing pulmonary complications, allowing early mobilisation and shortening the length of hospital stay.11,17,43

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


Analgesia following total knee arthroplasty.

Knee reconstruction

Trueblood, Andrew a,b; Manning, David W a,b
Abstract:
Purpose of review: Conventional methods of postoperative pain control for total knee arthroplasty include continuous epidural infusions of local anesthetic and patient-controlled intravenous narcotics. Dose-dependent side effects are common with these modalities and may result in limited effectiveness and decreased patient satisfaction. This review intends to detail recent advances in postoperative pain management after total knee arthroplasty.

Recent findings: Multimodal, or balanced, techniques for postoperative pain control have been described that simultaneously utilize multiple analgesics with different mechanisms of action, additive effects and decreased dose-related side effects. Narcotic side-effect-sparing modalities include the scheduled use of acetaminophen, nonsteroidal anti-inflammatory drugs, tramadol, cryotherapy, and the use of sustained-release oral narcotics. In addition, regional nerve block is a reproducible technique that provides more consistent and efficacious analgesia than patient-controlled intravenous narcotic therapy alone and is associated with fewer side effects than continuous epidural analgesia.

Summary: Regional nerve block coupled with nonnarcotic analgesics and combined long and short-acting oral narcotics decreases postoperative pain, allows for faster functional recovery, and decreases medication-related side effects. It may also shorten hospitalization and enhance patient satisfaction when compared with traditional approaches to postoperative pain management.
Does regional anaesthesia improve outcome after total hip arthroplasty? A systematic review

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2Present address: Department of Anaesthesia, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK
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Total hip arthroplasty (THA) is amenable to a variety of regional anaesthesia (RA) techniques that may improve patient outcome. We sought to answer whether RA decreased mortality, cardiovascular morbidity, deep venous thrombosis (DVT) and pulmonary embolism (PE), blood loss, duration of surgery, pain, opioid-related adverse effects, cognitive defects, and length of stay. We also questioned whether RA improved rehabilitation. To do so, we performed a systematic review of the contemporary literature to compare general anaesthesia (GA) and RA and also systemic and regional analgesia for THA. To reflect contemporary surgical and anaesthetic practice, only randomized controlled trials (RCTs) from 1990 onward were included. We identified 18 studies involving 1239 patients. Only two of the 18 trials were of Level I quality. There is insufficient evidence from RCTs alone to conclude if anaesthetic technique influenced mortality, cardiovascular morbidity, or the incidence of DVT and PE when using thromboprophylaxis. Blood loss may be reduced in patients receiving RA rather than GA for THA. Our review suggests that there is no difference in duration of surgery in patients who receive GA or RA. Compared with systemic analgesia, regional analgesia can reduce postoperative pain, morphine consumption, and nausea and vomiting. Length of stay is not reduced and rehabilitation does not appear to be facilitated by RA or analgesia for THA.

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Keywords: anaesthesia, general; anaesthetic techniques, regional; analgesia, postoperative; analgesic techniques, regional; surgery, orthopaedic
compared GA and RA for hip surgery used drugs that are no longer available. In the past two decades, surgical techniques and postoperative patient care have improved considerably, new thromboembolic prophylaxis regimes have been introduced, and RA has advanced as a result of enhanced needle technology, block placement techniques, catheter design, and infusion pumps. We have re-examined existing data for relevance and application to modern anaesthetic practice.

We have performed a systematic review of the literature, published from 1990 onwards, to ascertain if either RA was superior to GA or regional analgesia was superior to systemic analgesia for THA. The specific questions we sought to answer were whether, when compared with GA or systemic analgesia, RA or regional analgesia for THA decreased: (i) mortality, (ii) cardiovascular morbidity, (iii) deep venous thrombosis (DVT) and pulmonary embolism (PE), (iv) blood loss, (v) duration of surgery, (vi) pain, (vii) opioid-related adverse effects, (viii) cognitive defects, and (ix) length of stay. We also examined whether or not RA or regional analgesia improved rehabilitation.

Methods

Two of the authors (G.A.P. and R.B.) searched the electronic databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Clinical Trials (from January 1990 to October 2008) using the following population search terms: ‘total hip replacement’ OR ‘total hip arthroplasty’ OR ‘hip operation’. These search results were combined with ‘anaesthesia’ OR ‘analgesia’ using the Boolean search operator AND. The references of retrieved articles were hand searched for any relevant articles not identified in the original search.

The study selection criteria were limited to include only RCTs, English language, and human adults. Each abstract was screened to identify studies that had randomized patients to compare GA or RA for surgery. RCTs comparing systemic or regional techniques for postoperative analgesia were also included. Studies were excluded if surgery other than a joint arthroplasty was performed, or if both hip and knee arthroplasty were treated as one single study population and data on the patients undergoing knee surgery was not presented separately in the results. Studies using opioid-only neuraxial techniques were excluded. Finally, studies were excluded if the primary outcome was not included in the list described above.

The data were extracted onto a templated evidence-based medicine literature review form to assist in the systematic review of full-text articles and data collection. Data extracted for comparison included year of publication, author, total number of subjects, mean patient age, per cent male, and co-morbidity. The intervention (specific RA, regional analgesia technique, or both) and comparator (GA, specific systemic analgesia technique, or both) were recorded. The specific outcomes sought in each article were: (i) mortality, (ii) cardiovascular morbidity (myocardial infarction, arrhythmia, and hypotension), (iii) DVT, (iv) PE, (v) blood loss, (vi) duration of surgery, (vii) pain (pain scores and morphine consumption), (viii) opioid-related adverse effects (nausea, vomiting, pruritis, sedation, urinary retention, and respiratory depression), (ix) cognitive defects, (x) length of stay, and (xi) rehabilitation (range of motion and ambulation). It was noted whether each outcome was primary or secondary. Each outcome was then evaluated qualitatively for each intervention and comparator and the data were recorded in tables. Because there were a limited number of studies with homogenous design for each outcome, meta-analysis was not performed.

The methodological quality of each trial was assessed using several criteria. The likelihood of methodological bias of each RCT was assessed using the Jadad score, which assigns points based on three factors. One point was given to randomized studies, an additional point was given if the method of randomization was described and appropriate, and one point was deducted if randomization was inappropriate. One point was given if a study was double-blind, and an additional point was given if the blinding procedure was described and appropriate. One point was deducted if blinding was inappropriate. One point was given if the numbers and reasons for withdrawals were described. The maximum score is 5; trials scoring 3 or more are generally regarded as having satisfactory methodologic quality. Allocation concealment, which helps eliminate selection bias, was assessed and defined as adequate, unclear, or inadequate. Finally, whether patient follow-up rates were <80% was recorded.

After abstraction of information, a level of evidence was assigned to the outcomes of each RCT (Level I is a high-quality RCT; Level II is a lesser quality RCT, e.g., <80% follow-up, no blinding, or improper randomization). Two authors (A.J.R.M. and R.B.) independently reviewed and scored each RCT using this methodology.

Results

In total, 18 RCTs were identified that compared either GA vs RA, systemic vs regional analgesia, or both for THA (Fig. 1). Ten of these had a Jadad score of 2 or less. Allocation concealment was unclear in 13 trials and inadequate in one. Follow-up was adequate in all trials (Table 1). Two RCTs were considered to provide Level I evidence. In total, the studies included 1239 patients. A summary of the outcomes reported in each trial is provided in Table 2.

Mortality

There were no trials primarily designed to assess differences in mortality after GA or RA for THA. Only two
trials documented mortality as a secondary outcome (Level II). The follow-up period was 48 h in one study and 16 days in the other. There was only one death reported in 276 patients included in these two studies; no difference in mortality was detected between the groups in either study.

**Cardiovascular morbidity**

Six trials examined cardiovascular morbidity, although this was a primary outcome in only one trial. Hypotension was most commonly studied. GA combined with epidural anaesthesia (EA), when compared with GA alone, resulted in significantly more frequent hypotensive episodes, both at induction (41% vs 23%, \(P=0.0049\)) and intraoperatively (54% vs 35%, \(P=0.04\)). Intraoperative mean arterial pressure (80 vs 88 mm Hg, \(P=0.037\)) was also lower in the combined group (Level II). However, the effect of epidural analgesia on hypotension after operation varied, and in three trials, the frequency was either less (0% vs 33%, \(P=0.001\), Level I), greater (40% vs 13%, \(P=0.01\), Level II), or no different (Level II) when compared with patients receiving systemic analgesia.

The incidence of postoperative hypotension with continuous femoral nerve block was significantly less (0% vs 40%, \(P=0.01\), Level II) when compared with CEA. Continuous lumbar plexus block (CLPB), compared with systemic analgesia, did not affect the incidence of hypotension (Level II), again when studied as a secondary outcome however.

The incidence of bradycardia was assessed in two studies and was not significantly different with either CEA or CLPB when compared with systemic analgesia (Level II). Myocardial ischaemia or significant arrhythmias other than bradycardia was investigated in one study comparing GA with or without lumbar EA. There was no difference between the groups, up to 48 h after operation (Level II). (For further information, see Supplementary Table 3.)

**Deep venous thrombosis and pulmonary embolism**

The incidence of DVT and PE after THA was evaluated as a secondary outcome in two trials comparing GA with RA. In both of these trials, all patients received chemical thromboprophylaxis. When comparing EA and GA with GA alone, there was no difference in the incidence of DVT on postoperative days one to nine, with warfarin administered to all patients after operation (Level II). Spinal anaesthesia was compared with GA using three groups which differed with respect to administration of thromboprophylaxis. First, the GA group received preoperative enoxaparin, unlike the two spinal anaesthesia groups. Secondly, one of the spinal anaesthesia groups received enoxaparin 1 h after operation. All three groups received daily enoxaparin from 12 h after operation. Compared with the GA group, distal DVTs (measured 12–15 days after operation) were more frequent in the spinal anaesthesia group who did not receive enoxaparin at 1 h (11% vs 0%, \(P=0.013\), Level II). The incidence of proximal DVTs did not differ significantly between the three groups (Level II). This was the only study that examined the incidence of PE, again as a secondary outcome, but as this was zero in both RA and GA groups, no difference was detected (Level II).

**Blood loss**

Ten studies measured intraoperative blood loss. In four of these, intraoperative blood loss was reduced (ranging from 118 to 595 ml) by RA compared with either GA or systemic analgesia, whereas in the six others, there was no significant difference. Postoperative blood loss was recorded in seven trials. In two of these, postoperative blood loss was reduced (ranging from 140 to 517 ml) in the RA group compared with GA or systemic analgesia, whereas in the five others, there was no difference. Blood transfusion was reduced (range 1.3–1.7 units) in the RA group in two out of the five studies that measured this outcome. All studies were Level II evidence except one Level I study which demonstrated reduced intra- and postoperative blood loss using combined GA and LPB compared with GA alone. In no case was blood loss significantly greater in the RA group compared with GA or systemic analgesia. (For further information, see Supplementary Table 4.)

**Duration of surgery**

The duration of surgery was not influenced by the type of anaesthetic for THA (Level II).

**Postoperative analgesia**

We identified 11 RCTs comparing systemic and regional analgesia for THA and in all but one, regional analgesia reduced pain scores or morphine consumption. There was good evidence that, compared with...
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Anaesthesia</th>
<th>Analgesia</th>
<th>Age (yr)</th>
<th>% Male</th>
<th>Co-morbidity</th>
<th>Alloc Conceal</th>
<th>Jadad score</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becchi and colleagues⁵</td>
<td>37</td>
<td>SA</td>
<td>CPB*</td>
<td>69 (8)</td>
<td>43</td>
<td>ASA I–II; age 61–82</td>
<td>Adequate</td>
<td>11 001 (3)</td>
<td>Both CPB and i.v. infusion continued for 48 h; morphine and ketorolac; observors and patients adequately blinded but not investigators</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>SA</td>
<td>Systemic infusion*†</td>
<td>71 (11)</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siddiqui and colleagues⁵⁹</td>
<td>17</td>
<td>GA</td>
<td>CLPB*</td>
<td>59 (12)</td>
<td>41</td>
<td>ASA I–III; age 18–80; body mass index &gt;40 excluded</td>
<td>Adequate</td>
<td>11 001 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>GA</td>
<td>I.V. PCA*</td>
<td>52 (13)</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens and colleagues⁶⁴</td>
<td>22</td>
<td>SA</td>
<td>Fascia iliaca*</td>
<td>69 (10)</td>
<td>68</td>
<td>ASA I–III</td>
<td>Unclear</td>
<td>11 101 (4)</td>
<td>Modified fascia iliaca block— injection 1 cm above the inguinal ligament. Clonidine and bupivacaine 0.5% used for block</td>
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<tr>
<td></td>
<td>22</td>
<td>SA</td>
<td>Placebo*</td>
<td>67 (9)</td>
<td>50</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Eroglu and colleagues²¹</td>
<td>20</td>
<td>EA*</td>
<td>CEA</td>
<td>64 (13)</td>
<td>20</td>
<td>ASA I–III; patients with unstable angina, valvular disease, neurologic, or cerebrovascular disease excluded</td>
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<td>11 000 (2)</td>
<td>Hypotensive anaesthesia in both groups (mean arterial pressure 50–60 mm Hg); total i.v. anaesthesia for 48 h</td>
</tr>
<tr>
<td></td>
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<td>GA*</td>
<td>CEA</td>
<td>62 (10)</td>
<td>30</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Singelyn and colleagues⁶¹</td>
<td>16</td>
<td>GA</td>
<td>CFNB*</td>
<td>67 (11)</td>
<td>33</td>
<td>ASA I–II; age 18–80</td>
<td>Unclear</td>
<td>11 000 (2)</td>
<td>CFNB and CEA continued for 48 h</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>GA</td>
<td>CEA*</td>
<td>61 (13)</td>
<td>47</td>
<td></td>
<td></td>
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<tr>
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<td>34</td>
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<td>74 (9)</td>
<td>38</td>
<td>ASA I–III; age 50–85; weight 40–100 kg</td>
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<td>CEA</td>
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<td>18–80</td>
<td>50–90</td>
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<td>CEA continued for at least 44 h (duration of study); four patients in placebo CEA vs two in CEA received GA</td>
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<td>CEA continued for at least 44 h (duration of study); four patients in placebo CEA vs two in CEA received GA</td>
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<td>43</td>
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<td>I–III</td>
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<td>ASA 50</td>
<td>Epidural infusion continued for 24 h; boluses thereafter if required; removed at 48 h</td>
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<td>I–II</td>
<td></td>
<td>ASA 53</td>
<td>CEA continued for 48 h; I. Aprotinin 500 000 KIU preop and 500 000 KIU h⁻¹ intraoperatively; II. No aprotinin (placebo); III. Aprotinin 500 000 KIU preop and 500 000 KIU h⁻¹ intraoperatively; IV. No aprotinin (placebo)</td>
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<td>Uhrbrand and colleagues</td>
<td>GA</td>
<td>‘3 in 1’ block</td>
<td>93</td>
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<td>I. No additional enoxaparin; II. Enoxaparin 20 mg 1 h after SA; III. Enoxaparin 40 mg 12 h before GA; enoxaparin 12 h after operation and daily thereafter</td>
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ASA: American Society of Anesthesiologists; GA: General Anesthesia; LPB: ‘3 in 1’ block; PCA: Patient-Controlled Analgesia; EA: Epidural Anesthesia; CEA: Continuous Epidural Anesthesia; SA: Systemic Anesthesia; N/A: Not Applicable.
### Table 2: Outcomes and levels of evidence for each study included in the review

Arrows indicate whether the outcome is no different (→), better (↑), or worse (↓) with RA, regional analgesia, or both compared with GA, general anaesthesia, or both.

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<th>Analgesia</th>
<th>Outcomes (levels of evidence)</th>
<th>Mort</th>
<th>CVS</th>
<th>DVT</th>
<th>PE</th>
<th>Blood loss</th>
<th>Duration of surgery</th>
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<th>Adverse effects</th>
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<td>Fascia iliaca*</td>
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*Randomization groups. Mort, mortality; CVS, cardiovascular morbidity; DVT, deep venous thrombosis; PE, pulmonary embolus; Cog Def, cognitive deficit; LOS, length of stay; Rehab, rehabilitation; SA, spinal anaesthesia; CS, continuous spinal; CLPB, continuous lumbar plexus block; SNB, sciatic nerve block; GA, general anaesthesia; EA, epidural anaesthesia; FNB, femoral nerve block; CFNB, continuous femoral nerve block; R, ropivacaine; PCA, patient-controlled analgesia; CSE, combined spinal–epidural; CEA, continuous epidural analgesia; MC, morphine consumption; B, bupivacaine.
systemic analgesia, single-shot lumbar plexus block (LPB) reduced pain scores and morphine consumption but only for a short duration (Level I). Continuous LPB, however, was of benefit for up to 48 h compared with systemic analgesia (Level II). In three out of four trials, epidural analgesia provided superior pain relief compared with systemic analgesia. The analgesic benefit lasted from only 8 (Level I) to 48 h (Level II). Compared with a placebo injection, a modified fascia-iliaca block reduced morphine consumption up to 24 h, but not pain scores (Level II). Similarly, a ‘3 in 1’ block also reduced 24 h opioid consumption (Level II) compared with systemic opioid alone. Femoral nerve block alone, however, either as a single shot or continuous infusion was of no benefit. Continuous spinal analgesia reduced pain scores compared with systemic analgesia for the 24 h duration of the infusion (Level II). (For further information, see Supplementary Table 5.)

**Adverse effects**

Although all adverse effects were analysed as secondary outcomes, significant reductions in postoperative nausea (relative risk reduction 85–93%, Level II) and vomiting (relative risk reduction of 100%, Level I) were observed in favour of regional analgesia in four of the nine studies examining this outcome. In the other five studies, there was no difference between systemic and regional analgesia. There was no difference detected in the incidence of pruritis, sedation, urinary retention, or respiratory depression in the studies that examined these as secondary outcomes. (For further information, see Supplementary Table 6.)

**Cognitive deficit**

In the only trial that commented on postoperative cognitive deficit after THA, those patients who received EA had ‘superior mental clarity and cooperativeness’ compared with the GA group. The method of assessment for cognition was unclear.

**Length of stay**

Four studies measured length of stay (some including time spent in a rehabilitation centre) as either a primary or a secondary outcome, but there was no difference between regional (FNB, CFNB, and CEA) and systemic analgesia (Level II). (For further information, see Supplementary Table 7.)

**Rehabilitation**

Three studies examined rehabilitation. Outcome measures included daily hours of ambulation and activity scores, time to first ambulation, or the different ranges of movement about the hip joint. In all three RA, regional analgesia, or both provided no benefit compared with GA and systemic analgesia (Level II). These were all secondary outcomes, and two of the trials were also completely unblinded. (For further information, see Supplementary Table 8.)

**Discussion**

The aim of this systematic review was to examine contemporary RCTs, published from 1990 onwards, comparing either GA and RA or regional and systemic analgesia for THA. We found insufficient evidence from RCTs alone to conclude whether anaesthetic technique influenced mortality, cardiovascular morbidity, duration of surgery, or the incidence of DVT and PE in the setting of routine thromboprophylaxis. Blood loss may be reduced in patients receiving RA rather than GA for THA. RA does, however, reduce postoperative pain and also nausea and vomiting. Length of stay is not reduced and rehabilitation does not appear to be facilitated by RA or analgesia for THA.

Before further considering the implications of our review, we accept that there are several limitations. First, for practical reasons, we chose to include only English language trials. Although this may have introduced bias, it has been suggested that excluding trials not published in English has little effect on summary treatment effect estimates. Secondly, we found that 10 of the 18 RCTs evaluated herein had Jadad scores of 2 or less. This was primarily due to lack of any form of blinding in a number of the trials. Double-blinding can be difficult to institute when studying peripheral nerve blocks for systemic analgesia, especially in awake patients, as sham nerve blocks are often not performed for ethical reasons. The latter notwithstanding the Jadad score is effectively reduced automatically by 2 points for the lack of a double-blinded study design. Thirdly, there were no large (n>1000) trials identified. The studies included in the present review had sample sizes varying from only 22 to 210 patients. In trials with small numbers of subjects, the absence of ‘significant’ differences in secondary outcomes must be interpreted with caution as these studies are often inadequately powered to detect such differences. We took care to highlight secondary outcomes in the summary tables and these shortcomings are also reflected in the level of evidence scores (i.e. by definition, Level II). Finally, the purpose of this review was not to provide recommendations on the preferred mode of anaesthesia for THA. To do so would have required an assessment of harm and consideration of other information such as costs, quality of life, and feasibility. One major concern with RA for instance is the risk of nerve injury compared with GA. This is difficult to quantify and has been addressed elsewhere in the contemporary literature. As with any anaesthetic technique, patient co-morbidity and preference and also expertise of the anaesthesiologist must also be considered.

The lack of difference in mortality between GA and RA for THA is unsurprising given the safety of modern
anaesthetic and surgical practice. Much greater numbers than those included in the two RCTs that we identified would be required to demonstrate any difference.55 78 Furthermore, neither trial followed up patients beyond the study period (48 h and 15 days). A large meta-analysis comparing GA and CNB alone for a variety of surgery types found that overall mortality was reduced by one-third [odds ratio (OR) 0.70, 95% confidence interval (CI) 0.54–0.90] in patients allocated to CNB.86 When each group in this meta-analysis was analysed according to type of surgery, there was decreased mortality only in the orthopaedic subgroup.56 Interestingly, overall mortality was reduced whether or not CNB was continued after operation. Conversely, combined intraoperative GA and CNB negated the mortality benefit of CNB alone. In a retrospective review examining postoperative analgesia for THA, there was no difference in mortality when comparing epidural analgesia and systemic analgesia.77 These data suggest that intraoperative CNB alone may confer the most benefit. Indeed, in a meta-analysis comparing CNB with GA for hip fracture repair, CNB was shown to reduce 1 month mortality in patients undergoing hip fracture surgery.69 We recognize, however, that the latter meta-analysis of urgent hip fracture repair, arguably in a generally sicker group of patients, is not necessarily applicable to patients undergoing elective THA.

Only three trials examined cardiovascular morbidity other than hypotension, comparing either CLPB or epidural analgesia vs systemic analgesia, or EA and GA vs GA alone. Although there was no difference in the incidence of ischaemia or arrhythmia between the groups, this could have been the result of inadequate numbers of patients. In the meta-analysis described above, there was a reduction in the incidence of myocardial infarction in the epidural group, although the CI just reached zero.23 This significant difference was detected only when all surgical groups were combined and did not specifically apply to orthopaedic patients alone. Further RCTs with large numbers are required to examine whether RA reduces serious cardiovascular morbidity in elective THA.

We found no difference in the frequency of proximal DVT in the two trials that compared RA and GA, although both trials suffered from a combination of inadequate blinding, under-powering, or both.20 55 Although one trial found an increased incidence of distal DVT in the RA group compared with GA, the two groups were not truly comparable because enoxaparin was administered at different times in each group. Furthermore, the clinical importance of distal DVTs is arguably less than that for proximal clots. Our findings contrast with the results of a recent meta-analysis where patients undergoing THA with CNB compared with GA had a significantly lower risk of DVT (OR 0.27, 95% CI 0.17–0.42) and PE (OR 0.26, 95% CI 0.12–0.56).44 Importantly, however, among the five trials included in this meta-analysis, all were carried out before 1989 and none utilized routine thromboprophylaxis. Although it has been suggested that CNB may decrease the incidence of DVT either directly by enhancing lower extremity venous blood flow or by attenuating the prothrombotic effects of the stress response, further work is required to ascertain whether RA offers any additive benefit when used in combination with contemporary routine thromboprophylaxis. Indeed, one trial included in our review where all patients received chemical thromboprophylaxis, but which did not have DVT as an outcome, found no difference in laboratory measurements of coagulation between patients who received GA and RA.21 This lack of difference was similarly reflected in a further trial that did not meet our inclusion criteria but compared haemostatic markers in patients undergoing THA with either GA or spinal anaesthesia.13 Again, patients received chemical thromboprophylaxis. Although no difference occurred between GA and RA in the one trial that examined the incidence of PE, both the method of randomization and diagnosis of PE were unclear and there was no blinding of observers.55

Four trials demonstrated reduced blood loss in THA with RA, whereas in six there was no difference. A recently published meta-analysis found that CNB for THA reduced the likelihood of transfusion by three-quarters (OR 0.25, 95% CI 0.11–0.53), although seven of the 10 trials included in this analysis were published before 1990 and may not reflect current surgical or anaesthetic practice.28 Interestingly, in this meta-analysis, no difference in intraoperative blood loss was detected between RA and GA. This contrasts with a meta-analysis which found a reduction in intraoperative blood loss by 275 ml per case (95% CI 180–371 ml) in the RA group.44 Again, however, of the eight (some quasi-randomized only) trials included, seven were published before 1990. With the variety of anaesthetic, analgesic, and thromboprophylaxis regimes in the 10 trials included in our review, results were not homogeneous enough to pool. Three trials did compare combined EA and GA vs GA, but even here there was a confounding factor, such as a statistically significant difference in arterial pressure between the groups. With the use of restrictive transfusion strategies now commonplace, and many patients now participating in preoperative blood conservation therapies, it may become more difficult to demonstrate a significant reduction in transfusion requirements in primary arthroplasty if the prevalence of blood transfusion decreases, particularly if this endpoint is studied as a secondary outcome.

In contrast to our findings, a recent meta-analysis demonstrated a modest, but significant, decrease in surgical time with CNB compared with GA for THA.44 It is noteworthy that the definition of operating theatre time may vary, and the majority of the studies we reviewed did not consider the total time including anaesthetic intervention. A ‘block room’ or anaesthesia induction room, where RA is performed before patient transfer, can increase efficiency and boost cost-savings by reducing anaesthesia-related time.1 62 74 75
Our review found that regional analgesia reduced post-operative pain in THA. The purpose of our review was not to specifically compare the different RA or analgesia techniques for THA. This has been addressed elsewhere. Choi and colleagues recently published a meta-analysis comparing postoperative epidural analgesia with systemic analgesia after THA or total knee arthroplasty (TKA) and concluded that epidural analgesia provided better pain relief for up to 6 h after operation compared with systemic analgesia. All patients, however, whether THA or TKA, were analysed together, despite important differences in the severity of postoperative pain between these two surgical procedures. Although when THA is examined independently, we found that pain scores were reduced for up to 48 h. The sole trial of Level I quality demonstrated that the benefit of epidural analgesia was in fact only evident for 8 h. LPB appeared to be of benefit but are arguably associated with more serious complications than other peripheral nerve blocks such as femoral block. The lack of benefit of femoral block alone, however, compared with either fascia iliaca or '3 in 1' blocks is not unsurprising because this block does not provide anaesthesia to the lateral cutaneous nerve of the thigh which innervates the site of skin incision in THA. Although continuous spinal analgesia can provide reliable, titratable anaesthesia and analgesia, this is not yet used widely due to frequent technical difficulties, requirement for closer ward monitoring, and fears of complications such as cauda equina syndrome.

Like postoperative pain, opioid-related adverse effects, especially nausea and vomiting, are a major concern to patients and can delay discharge from hospital. Unfortunately, however, opioid-related adverse effects are almost never investigated as a primary outcome. Despite this, we found, primarily Level II evidence, that single shot and continuous LPB, continuous spinal analgesia, and epidural analgesia (Level I) reduced postoperative nausea and vomiting. A reduction in morphine consumption was not always associated with a reduction in adverse effects, but this may be due to inadequate powering. The five RCTs in which no benefit was observed were all graded as Level II. These were either inadequately powered or had poor methodological quality.

We found that RA or regional analgesia does not appear to significantly shorten length of stay in hospital or hasten postoperative rehabilitation for THA. This apparent lack of sustained benefit in the setting of THA is quite different from RCTs examining the TKA population, which is likely due to rapidly decreasing pain after THA in comparison with TKA. Furthermore, postoperative physiotherapy in TKA can exacerbate pain severity. Finally, many centres performing major joint surgery now implement clinical pathway protocols. It may become increasingly difficult to detect differences in length of stay based on mode of anaesthesia as streamlined care often results in all patients being discharged at similar times.

In conclusion, we found insufficient evidence from RCTs alone to conclude whether anaesthetic technique influenced mortality, cardiovascular morbidity, duration of surgery, or the incidence of DVT and PE in the setting of routine thromboprophylaxis. Our systematic review does suggest that blood loss may be reduced in patients receiving RA rather than GA for THA. Regional analgesia does, however, reduce postoperative pain and also nausea and vomiting. Length of stay is not reduced and rehabilitation does not appear to be facilitated by RA or analgesia for THA. Sixteen of the 18 RCTs identified were of Level II quality and therefore further work is required to investigate whether RA influences the majority of outcomes after THA.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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The survey by Meikle and colleagues published in this month’s *British Journal of Anaesthesia* highlights the uncommon but catastrophic complication of epidural haematoma. Although the incidence of symptomatic epidural haematoma may appear small, amounting, they suggest, to one case every 2 yr in the UK, it appears that the use of epidural infusions is increasing, alongside an increase in prophylactic anticoagulation and low-dependency care of patients with indwelling epidural catheters. The results of this survey indicate that the incidence of epidural haematoma may, in fact, be significantly higher than suggested by reported cases, and the ongoing national audit by the Royal College of Anaesthetists may give us a better indication of the true risk of this complication.

Similar catastrophic injury may result also from epidural abscess, which has been reported in one UK hospital to occur with a frequency of 1 in 800, when epidural catheters were inserted for postoperative pain management. Our experience from forensic practice is that Meikle (and previous authors) underestimate the incidence of epidural haematoma considerably, but that the experience of Phillips and colleagues overestimates the risk of abscess nationally. The incidence of epidural haematoma and abscess probably varies in different patient populations; Scott and Hibbard reported two haematomas and one abscess after 505 000 epidural blocks in obstetric practice. The incidence in higher risk patients is likely to be greater. For example, Ngan Kee and colleagues reported a higher incidence after thoracic epidural analgesia and Okano and colleagues noted 11 out of 30 patients with epidural abscesses had an underlying illness or were receiving steroid therapy.

Two of us (A.R.A. and J.G.H.) have encountered, in medicolegal practice, 11 cases of epidural haematoma in an 11 yr period (the events occurred between 1997 and 2007) and eight cases of epidural abscess in a 10 yr period (between 1995 and 2004). Failure to discontinue epidural infusions after the presentation of new neurological signs (especially leg weakness) and failure to recognize the urgency of diagnosis and surgery after suspicion of epidural haematoma appear frequently in such cases. In contrast to epidural haematomas, which usually present during the epidural infusion, abscesses often present late and after the patient has left hospital, but for those which present before discharge and for the large majority of epidural haematomas, our experience is that there is usually a significant delay before diagnosis because junior surgical trainees, inexperienced anaesthetists, or both wrongly attribute the onset of weakness and increasing numbness to the effects of the local anaesthetic. The infusion is usually continued for hours, and sometimes for several days, before the opinion of an experienced anaesthetist is sought, resulting in permanent neurological damage. It is impossible to educate all trainee surgeons and nurses to recognize the significance of these clinical signs, and we agree that strict protocols offer the best solution to early diagnosis, investigation, and treatment.

Although reporting-bias affects the incidence calculated from reported cases, examination using closed-claim analysis has similar flaws. Closed-claim analysis allows a glimpse of cases that would usually not be reported. However, the technique must also underestimate the true incidence of complications because not all patients who suffer complications sue. Patients who decide to sue have usually suffered a significant and long-lasting injury, and have been able to secure funding for their claim. In addition, the true incidence of a complication which leads to litigation cannot be estimated accurately from the experience of two individuals. The number of other patients who have entered litigation proceedings in relation to epidural haematoma or abscess in the UK in the last 10–11 yr is unknown.

Another method of estimating the extent of damage caused by specific anaesthetic techniques is to consider the costs of claims handled by large insurance or indemnity organizations. Between April 1995 and October 2005, the Clinical Negligence Scheme for Trusts (CNST), which deals with litigation for all NHS hospitals in England, handled 251 claims associated with epidural blocks.
The claims had a total value of £32,346,737 (an average of £128,871 each). There were lower incidences of brain damage and fatality in claims related to epidural block than in those associated with general anaesthesia. However, there were higher incidences of nerve damage, paraplegia, partial paralysis, spinal damage, and unnecessary pain. We have been unable to establish how many of these claims were related to delay in recognizing the symptoms and signs of epidural haematoma or abscess, but the size of the settlements suggests that the proportion of these 251 patients suffering debilitating neurological injury was not inconsiderable.

Meikle and colleagues recommend that patients should receive neurological observations at least every 4 h and that these observations should continue for at least 24 h after removal of the epidural catheter. This recommendation seems valid in view of the previously reported cases of haematoma and abscess formation after catheter removal. Every department should have readily available written guidelines regarding the use of neuraxial techniques in patients with potentially altered coagulation.

The authors also recommend the cessation of the epidural infusion after the presentation of new neurological signs, with suspicion of epidural haematoma if these signs do not resolve. The authors do not recommend a minimum time interval between the suspicion of haematoma or the cessation of the infusion and MRI scanning; we suggest that no more than 4 h should elapse between the onset of new neurological signs and MRI scanning, and this scan (and ideally, the patient) should be assessed by an expert. Should there be a delay in stopping the epidural infusion after the presentation of new signs, then MRI scanning may need to take place before the local anaesthetic effect of the epidural may be expected to resolve.

In hospitals without expertise to carry out surgical decompression, protocols and procedures need to be in place to ensure that patients are transferred to a unit where surgery can be performed within 12 h of the onset of weakness or increasing numbness to optimize the chance of recovery. In the absence of focal neurological signs, conservative management of epidural abscess may be successful but frequently urgent surgical evacuation is required.

Owing to the low incidence of epidural haematoma, we will never be in a position to introduce true, evidence-based practice. Even if studies of sufficient size are conducted, their relevance will be limited by constant evolution in practice. Thus, we are obliged to apply common-sense and learning to help our patients avoid a life-damaging event. The relative rarity of epidural haematoma and abscess means that expensive and laborious additions to current practice are not appropriate, but the simple measures suggested by Meikle and colleagues need not be expensive or laborious, and we wholly commend them to practising anaesthetists in the UK. It is likely that the introduction of strict protocols would minimize or prevent the development of permanent and disabling neurological injury in a considerably larger number of patients than they suggest.

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References
Editorial II

NICE and warm

Inadvertent perioperative hypothermia, defined as core body temperature $\leq 36.0^\circ\text{C}$, is a common consequence of anaesthesia. Its adverse effects are well known to anaesthetists and include greater intraoperative blood loss and consequent blood transfusion. After operation, inadvertent perioperative hypothermia can lead to an increased rate of wound infection, morbid cardiac events, and pressure sores, and also a longer stay in both recovery and hospital. These are apart from the subjective discomfort and wound pain which cold and shivering may cause the patient. Significantly, maintaining normothermia perioperatively can modify these adverse effects.

Despite this knowledge, implementation of warming strategies remains patchy. An audit in the hospital of one of the authors (C.M.H.) indicated that there is an incidence of inadvertent perioperative hypothermia in the region of 20% and that there is inconsistency in the methods of warming used. There are no active temperature management protocols and, as with anything that may cost money, there is resistance to more aggressive prevention of inadvertent perioperative hypothermia on economic grounds. In the USA, where there are guidelines, compliance remains poor. It has been suggested that there are a number of factors contributing to this: a misguided belief that forced-air warming can increase the rates of infection, surgeons’ complaints of discomfort, inconsistent monitoring (hindered by the inconsistency between different thermometers and sites of measurement), and a simple lack of appreciation of the causes and consequences of inadvertent perioperative hypothermia. Additionally, even where there are standards such as those of the American Society of Anesthesiologists (ASA), they are criticized for being vague and giving flexibility at the expense of clear guidance.

Recognizing the significance of inadvertent perioperative hypothermia and the deficiencies in current practice in the UK, the National Institute for Clinical Excellence (NICE) convened a guideline development group to address the issue. This culmination of the group’s work came with the publication of the ‘Management of inadvertent perioperative hypothermia in adults’ guideline.

The guidance is divided into the pre-, intra-, and post-operative phases. Before operation, the key recommendations are that a formal assessment of the risk of hypothermia should be undertaken for each patient and that patients themselves should be empowered by being given information that will help them minimize that risk. Another important element is that the temperature should be measured in the hour before surgery. Should it be $<36.0^\circ\text{C}$, unless the operation is life or limb saving, active warming should be initiated until such time as the patient is normothermic.

Intraoperatively, the recommendations are that forced-air warming is commenced as early as possible, preferably in the anaesthetic room, for any patient having surgery with an anaesthetic time (i.e. from first anaesthetic intervention to arrival in recovery) of $>30$ min, or who has two or more risk factors for inadvertent perioperative hypothermia. I.V. fluids should be warmed when $>500$ ml is to be given. These recommendations therefore encompass the majority of operations and infusions.

Monitoring is an integral part of perioperative thermal management and one that remains neglected. The guide recommends that core temperature should be recorded at
A Comparative Study of Sequential Epidural Bolus Technique and Continuous Epidural Infusion

Kenichi Ueda, M.D.,* Wasa Ueda, M.D., Ph.D.,† Masanobu Manabe, M.D., Ph.D.‡

Background: In this randomized, double-blind study, the authors compared the effectiveness of a sequential epidural bolus (SEB) technique versus a standard continuous epidural infusion (CEI) technique of local anesthetic delivery. Both techniques used the same hourly dose of local anesthetic.

Methods: Sixteen gynecologic patients undergoing abdominal surgery received postoperative epidural analgesia using 0.75% ropivacaine at a dose of 22.5 mg (3 ml) per hour. Patients were randomly assigned to one of two groups. In the SEB group (n = 8), patients received one third of the hourly dose every 20 min as a bolus. In the CEI group (n = 8), the hourly dose was administered as a continuous infusion. Analgesia was assessed by rest pain scored by a visual analog scale and pinprick to determine the number of separately blocked spinal segments on each side of the body. Doses of rescue medication for pain were also recorded.

Results: The median number of blocked spinal segments was 19.5 (range, 18–24) in the SEB group and 11.5 (range, 10–18) in the CEI group (P < 0.001). The median difference in the number of blocked segments between the right and left sides was 0 (range, 0–1) in the SEB group and 2 (range, 0–6) in the CEI group (P < 0.04). No patients in the SEB group but one patient in the CEI group required rescue medication for pain. The visual analog scale pain score was 0 in both groups except for one patient in the CEI group during the study period.

Conclusion: The SEB technique with ropivacaine provides superior epidural block compared with an identical hourly dose administered as a continuous infusion.

CONTINUOUS epidural analgesia now plays an important role in postoperative pain control. In the standard continuous epidural infusion technique (CEI), the initial dose establishes the requisite extent of analgesia, and then continuous infusion preserves it. Over time, however, some patients experience diminution of analgesia, characterized by a reduction in the number of blocked spinal segments and development of unequal right and left blockade. In such cases, additional top-up doses are necessary. The development of patient-controlled epidural analgesia (PCEA) permitted patients to superimpose a limited volume of bolus dosing on continuous infusion. PCEA was first applied to obstetrics and was then found to be effective in postoperative pain control that requires a steady level of analgesia.

Interestingly, patients with PCEA required less local anesthetic than did patients with continuous epidural infusion (CEI) to achieve a similar quality of epidural analgesia. Further, Sia and Chong found that PCEA could provide satisfactory epidural analgesia even when the background infusion was eliminated. These findings caused us to hypothesize that an intermittent bolus administration with regular intervals independent of patient demand could be superior to CEI for producing epidural sensory block with better quality. To test this new epidural delivery mode, we provided postoperative epidural analgesia by two different techniques, using identical hourly doses of local anesthetic. One group of patients received the standard CEI technique. The other group received a sequential epidural bolus technique (SEB) in which one third of the hourly dose was administered every 20 min.

Materials and Methods

The study protocol was approved by the Ethics Committee of the Kochi Medical School (Kochi, Japan) and written informed consent was obtained from each patient. The study group consisted of 16 gynecologic patients with American Society of Anesthesiologists physical status I or II who were scheduled to undergo lower abdominal surgery. None of the patients had previous experience with epidural analgesia.

All patients received standardized anesthetic care by the same anesthesiologist for the surgery. Oral midazepam, 10 mg, was administered 1 h before surgery. The epidural catheter (18 gauge; Portex, Kent, United Kingdom) was placed before induction of anesthesia, with the patient in the right lateral decubitus position, at the T11–T12 or T12–L1 spinal interspace using the paramedian approach. General anesthesia included mask induction with sevoflurane, tracheal intubation, and maintenance with 1.0% end-tidal concentration of isoflurane in oxygen. Muscle relaxation was facilitated with vecuronium. No opioids were administered. After induction of general anesthesia, an initial epidural dose of 8 ml lidocaine, 2%, with 1,200,000 epinephrine was administered. Thereafter, 1 ml lidocaine, 2%, with 1,200,000 epinephrine was given as a bolus every 10 min until the end of the surgery. If a patient showed any reaction to the surgical maneuvers that required more than 1.2% end-tidal concentration of isoflurane to control, we eliminated the case from the study because of failed epidural block.

At the end of surgery, patients were given either SEB or CEI according to a computerized random-number generator. Both groups received 0.75% ropivacaine at a dose of 3 ml/h. In the SEB group (n = 8), ropivacaine was...
given as a sequential epidural bolus of 1 ml every 20 min. In the CEI group (n = 8), ropivacaine was given as a continuous epidural infusion. Patients were blinded to the drug administration technique. On arriving at the postanesthesia care unit, patients were asked to rate their pain experience on a visual analog scale (VAS). Only rest pain was assessed by nurses who were not aware of this study. The patients stayed in the postanesthesia care unit for 3 h to confirm that the pain control was adequate. In the ward, the patients were allowed to take diclofenac suppositories as rescue medication from an independent nurse.

An independent nurse in the ward assessed vital signs and rest pain score by VAS every 4 h. If a patient experienced hypotension, bradycardia, or bradypnea, epidural infusion was discontinued and the acute pain service team was called for assessment. Hypotension was defined as a systolic blood pressure of less than 90 mmHg, bradycardia was defined as a heart rate of less than 50 beats/min, and bradypnea was defined as a respiratory rate of less than 10 breaths/min.

Anesthesiologists who were unaware of the infusion mode visited the patients after the 15 h of ropivacaine infusion. Using a dermatome chart, the extent of analgesia was judged by the number of blocked spinal segments as determined by the pinprick method.

To produce the SEB mode, we modified the program of the standard infusion pump (SP-80RS; Nipro, Osaka, Japan) so that the pump divided the hourly dose into three parts and infused each every 20 min as a bolus (bolus rate of 500 ml/h).

Statistics

A pilot study with 12 patients showed the number of blocked spinal nerve segments to be 21 ± 3 (mean ± SD) in the SEB group and 13 ± 3 in the CEI group. The sample size to give a power of 0.8 with an α of 0.05 was 4 when the expected difference was 8 ± 3. The difference in the number of blocked segments between the right and left sides was 0 ± 0 in the SEB group and 3 ± 2 in the CEI group. The sample size to give a power of 0.8 with an α of 0.05 was 7 when the expected difference was 2 ± 1. Therefore, we decided to use a sample size of 16. The measured data were rejected by normality test, so we compared the two groups by Mann–Whitney rank sum test. Statistical analysis with SigmaStat 3.0 (SPSS Inc., Chicago, IL) yielded a significant probability value of less than 0.05. Continuous data are expressed as medians, with the ranges given in parentheses.

Results

Table 1 shows the demographic data of the patients studied. There was no statistical difference in the physical status between the two groups. Surgical epidural block was successful in all patients. No patient in either group had hypotension, bradycardia, or bradypnea during the study.

Figure 1 shows the extent of sensory blockade obtained after the 15 h of epidural infusion in the study. SEB produced a larger band of sensory blockade. The median number of blocked spinal nerve segments in the SEB group was 19.5 (range, 18–24), and that in the CEI group was 11.5 (range, 10–18) (P < 0.001). SEB also significantly improved equal right and left distribution of sensory blockade. The median difference in the number of blocked spinal segments between the right and left sides, expressed by spinal nerve segment, in the SEB group was 0 (range, 0–1), and that in the CEI group was 2 (range, 0–6) (P < 0.04).

One patient in the CEI group required rescue medication for left lower abdominal pain. In this patient, there was a significant difference between the right and left side analgesia, with segments T8–L2 blocked on the

<table>
<thead>
<tr>
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<th>SEB Group</th>
<th>CEI Group</th>
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<tr>
<td>Age, yr</td>
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Values are presented as mean or n, with range in parentheses.

ASA PS = American Society of Anesthesiologists physical status.

Table 1. Demographic Data of the Patients Studied

Fig. 1. Extent of sensory blockade after 15 h of epidural infusion. In the sequential epidural bolus (SEB) group (n = 8), 0.75% ropivacaine was given as a sequential epidural bolus of 1 ml every 20 min. In the continuous epidural infusion (CEI) group (n = 8), 0.75% ropivacaine was given as a continuous epidural infusion. The median number of blocked spinal segments was 19.5 (range, 18–24) in the SEB group and 11.5 (range, 10–18) in the CEI group (P < 0.001). The median difference in the number of blocked segments between the right and left sides was 0 (range, 0–1) in the SEB group and 2 (range, 0–6) in the CEI group (P < 0.04).
right side but only T9–T11 on the left side. Accordingly, the pain score at rest by VAS was 0 in both groups, except for one patient in the CEI group who scored 3 as the maximum VAS score during the study.

Discussion

In this study, local anesthetic administered as a sequential epidural bolus (SEB) provided greater longitudinal extension of sensory blockade than continuous epidural infusion (CEI). The SEB technique also improved equal right and left distribution of sensory blockade compared with CEI. We propose some possible explanations.

First, the bolus technique may have a different mode of spread through the epidural space as compared with continuous infusion. It is known that some of the epidural local anesthetic is captured by perineural tissue or removed by blood vessels, making it unavailable for nerve block. A bolus of local anesthetic likely spreads further longitudinally and bilaterally before such capture occurs than does continuous infusion.

It seems unlikely that only a 1-ml bolus of local anesthetic would make such a significant difference as compared with continuous infusion. Nonetheless, 1 ml contrast medium (iodotrolan, 240 mg I/ml) when given as a bolus can clearly appreciate an extended area in the epidural space (fig. 2). This is impossible by continuous infusion of the medium. Yokoyama et al.9 showed that the behavior of the local anesthetic and contrast medium inside the epidural space were well correlated. Therefore, bolus dosing has the potential to increase the spread of local anesthetic in the epidural space, and a bolus as small as 1 ml, as used in the current study, might have contributed to the success of SEB.

Second, proper timing of epidural dosing is key to maintain effective analgesia. If diminution of the epidural blockade occurs, sensory neural input to the spinal cord has been shown to accelerate the decline of the block.10 If this occurs, a larger dose of local anesthetic is required to restore analgesia. If instead the same dose of anesthetic is used before decay of analgesia, the extent of analgesia may increase.11 In the current SEB, the bolus administration might have occurred at regular intervals before decay of sensory neural block, thereby increasing the number of sensory-blocked spinal segments.

Ropivacaine, 0.75%, produced profound neural block sufficient to control pain without the help of opioids in the current study. Epidural analgesia has commonly been induced with local anesthetic combined with opioids to increase the quality of analgesia. Adverse effects of opioids, however, have the potential to cause complications.12 To avoid such adverse effects and also to clearly define the range of sensory neural block, we performed epidural block exclusively by local anesthetic. The concentration was decided according to the recommendation by Sakura et al.13; concentration determines the intensity of sensory block such that a high concentration and a small volume, rather than a low concentration and a high volume, are suitable when profound neural blockade is required. The volume given to the current patients was to achieve sufficient analgesia with CEI and thereby caused no difference in VAS pain score between the SEB and CEI groups. Because the range of blocked segments was so extended with SEB, it may be possible to reduce the dose of the anesthetic in SEB. Further studies are needed to establish the optimal timing, concentration, and volume of anesthetic for SEB in various conditions.

There are limitations to our study design. First, we evaluated the epidural-blocked segments at only a single data point (15 h). We did not study a longer duration of infusion. This may have been insufficient to ascertain the effects of SEB. Secondary, the lidocaine used for surgical anesthesia could have affected our results. We believe this is unlikely because effective surgical analgesia by 2%
Lidocaine with epinephrine lasts for 2–3 h at the most. After 15 h, the residual effect of lidocaine is negligible.

Another issue is whether SEB is economical. SEB requires a special infusion pump. To produce the SEB mode, we modified the operating program of a computer-controlled syringe pump for this study. Multipurpose infusion pumps equipped with various infusion modes currently available allow SEB in clinical practice. Such pumps are more expensive than pneumatic infusion pumps. However, an electrical pump uses a disposable plastic reservoir with tubing, which is less expensive and, as a medical waste product, less bulky than a disposable pneumatic infuser. As a whole, the expense associated with the infusion pump may not be a drawback of SEB.

SEB would have the potential to replace CEI in various situations. SEB can be applied to epidural anesthesia during surgery. Also, it can be combined with PCEA. Still, the possibility of local anesthetic overdose by programmed dose administration necessitates careful selection of dose and interval and continued assessment by the anesthesiologist.

In conclusion, SEB improved the quality of sensory blockade as compared with continuous epidural block in this study. This infusion mode has the potential to increase the extent of sensory blockade as well as to decrease unilateral blockade, thereby improving the reliability of epidural analgesia in postsurgical pain control.

The authors thank Masataka Yokoyama, M.D. (Associate Professor of Anesthesiology, Okayama University School of Medicine, Okayama, Japan), for his help in providing epidurographic pictures. The authors also thank William Hammonds, M.D. (Professor), and Alan Ross, M.D. (Associate Professor, Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa), for helpful comments in the preparation of the manuscript.

References

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Population Pharmacokinetic–Pharmacodynamic Modeling of Epidural Anesthesia

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Background: In previous studies, the authors reported on the absorption and disposition kinetics of levobupivacaine and ropivacaine. The current study was designed to develop a population pharmacokinetic–pharmacodynamic model capable of linking the kinetic data to the analgesic effects of these local anesthetics (i.e., sensory neural blockade).

Methods: A disposition compartmental model was fitted to concentration data of the intravenously administered deuterium-labeled anesthetics, and a model consisting of two parallel absorption compartments and the identified disposition compartments was fitted to concentration data of the concomitantly epidurally administered unlabeled anesthetics. The epidural segments were modeled by individual central and peripheral absorption compartments and effect sites, which were fitted to the simultaneously acquired pinprick data. A covariate model incorporated the effects of age.

Results: The threshold for epidural anesthesia increased from the lower to the higher segments. The central effect compartment equilibration half-lives were approximately 15 min for levobupivacaine and 25 min for ropivacaine. For levobupivacaine, age reduced the equilibration half-lives at all segments; for ropivacaine, age increased the anesthetic sensitivity at segments T12 and higher.

Conclusions: A population pharmacokinetic–pharmacodynamic model was developed that quantitatively described sensory blockade during epidural anesthesia, including the effects of age. The model may be useful to individualize dose requirements, to predict the time course of sensory blockade, and to study new local anesthetics.

EPIDURAL anesthesia is obtained by the injection of a local anesthetic drug into the epidural space. The clinical characteristics of the ensuing sensory neural blockade, such as onset time, intensity, and duration, depend directly on the changes in the concentration of the local anesthetic at the axonal membrane, which are dependent on pharmacokinetic factors. The rate of systemic absorption of local anesthetics gives some indication of the relation between neural blockade and the amount of drug remaining at or near the site of injection. In the past two decades, we indirectly assessed epidural drug concentrations by estimation of the time course of systemic absorption from the epidural space in humans.1–5

In our previous studies, the pharmacokinetic data were analyzed for each individual separately. However, population pharmacokinetic–pharmacodynamic (PK–PD) analysis of epidural anesthesia is important because it enables the description of both within- and between-subject variability, enables the development of predictive models, and, consequently, improves therapeutic outcome.6 Schnider et al.7 developed a population pharmacodynamic model to describe the time course and blockade level of spinal anesthesia. The objective of the current study was to develop a population PK–PD model of epidural anesthesia based on pharmacokinetic absorption profiles. In a first attempt, we applied the model to levobupivacaine and ropivacaine data and determined the impact of age on the model parameters.

Materials and Methods

Study Design

For the development of the epidural PK–PD model, data were used from two previous studies5,8 on the epidural injection of levobupivacaine and ropivacaine (see table 1 for patient characteristics). In these studies, arterial blood samples were obtained before, during, and after the epidural injection of the local anesthetic (at the L3–L4 interspace; table 2). The maximum duration of sampling was 24 h. When after epidural injection satisfactory anesthetic conditions (i.e., the presence of a bilateral sensory blockade, assessed by pinprick) were obtained (usually 15–25 min after the injection), the same but now deuterium (D2H3)-labeled local anesthetic was administered intravenously (table 2). Blockade assessments were made every 5 min during the first 30 min, every 15 min for the next 3.5 h, and subsequently every 30 min for the next 6 h. Refer to our previous publications for further details. For the current study, there were no additional protocols that needed approval of an institutional review board.

Development of the Pharmacokinetic Model

The reanalysis of the pharmacokinetic data from the previous studies had two aims: (1) to obtain popula-
PK-PD MODELING OF EPIDURAL ANESTHESIA

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Sex, No. F/M</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>No. PK</th>
<th>No. PD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levobupivacaine</td>
<td>8/19</td>
<td>55.9 ± 20.0</td>
<td>76.9 ± 16.4</td>
<td>173 ± 9.82</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2/22</td>
<td>54.3 ± 16.8</td>
<td>79.7 ± 12.1</td>
<td>177 ± 8.16</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>All</td>
<td>10/41</td>
<td>55.1 ± 18.4</td>
<td>78.2 ± 14.5</td>
<td>175 ± 9.19</td>
<td>51</td>
<td>48</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number of patients where appropriate.
* For some of the patients, there were pharmacokinetic (PK) but no pharmacodynamic (PD) data available.

tion pharmacokinetic models for the local anesthetics levobupivacaine and ropivacaine together with a covariate analysis (to enable individualization at the pharmacokinetic level) and (2) to obtain optimal individual absorption parameters for a pharmacodynamic model that describes the effects of those anesthetics on sensory blockade (and to enable individualization on the pharmacodynamic level). The pharmacokinetic analysis was performed in four steps: (1) A three-compartment structural model was fitted to the concentration data of the intravenously administered labeled local anesthetics (fig. 1). (2) A model including covariate age was developed. (3) A model, consisting of two parallel absorption compartments and the model of disposition developed in step 2, was fitted to concentration data of the epidurally administered unlabeled local anesthetic (fig. 1; note that the disposition parameters were fixed to their empirical bayesian [see Statistical Analysis section] values obtained in step 2). (4) A model including covariate age was developed.

The absorption compartments were characterized by the following parameters: \( F_i \), \( F'_i \), \( t_{\text{a},1} \), and \( t_{\text{a},2} \), denoting the fractions absorbed and absorption half-lives of the two compartments. We used a parameterization with \( F \) and \( F'_i \) where \( F_i = F \cdot F'_i \) and \( F_2 = F \cdot (1 - F'_i) \), because \( F \), the total absorption, should be around 1, and interindividual variability in \( F_i \) is likely to be counteracted by approximately the same variability in \( F_2 \).

Development of the Pharmacodynamic Model

The Epidural Segments. Each segment was modeled by its own central and peripheral absorption compartments (fig. 1). After a unit dose, the amount of anesthetic in a central absorption compartment \( A_c(t) \), is given by

\[
A_c(t) = F_i \cdot \exp(-k_{a1} \cdot t) + F_2 \cdot \exp(-k_{a2} \cdot t),
\]

with \( k_{a1} = \log(2)/t_{\text{a1}} \) and \( k_{a2} = \log(2)/t_{\text{a2}} \) for convenience. The concentration \( C_e(t) \) in a central absorption compartment after a dose consisting of amount \( A \) (fraction of total dose; see Main Assumptions section) of anesthetic is then described by

\[
C_e(t) = f_1 \cdot \exp(-k_{a1} \cdot t) + f_2 \cdot \exp(-k_{a2} \cdot t).
\]

With \( f_1 = F_i \cdot A/V_e \) and \( f_2 = F_2 \cdot A/V_e \), where \( V_e \) is the volume of that central absorption compartment. Effect sites were postulated to exist at each segment to account for lags between the absorption compartment concentration and effect, quantified by equilibration rate constant \( k_{e0} \). The effect site concentration \( C_e(t; k_{e0}) \) is then given by

\[
C_e(t; k_{e0}) = \frac{f_1 \cdot k_{e0}}{k_{e0} - k_{a1}} \cdot (\exp(-k_{a1} \cdot t) - \exp(-k_{e0} \cdot t))
\]

\[
+ \frac{f_2 \cdot k_{e0}}{k_{e0} - k_{a2}} \cdot (\exp(-k_{a2} \cdot t) - \exp(-k_{e0} \cdot t))
\]

Epidural blockade (analgesia with respect to pinprick) was assumed to occur when \( C_e(t; k_{e0}) \) exceeds a concentration threshold \( C_{\text{thr}} \) (fig. 1).

Types of Observations. The acquired pharmacodynamic data contained three types of observations:

1. an interval \( (t_{\text{on}}, t_{\text{off}}) \) with \( C_e(t_{\text{on}}; k_{e0}) \geq C_{\text{thr}} \) where a blockade occurred, and \( C_e(t_{\text{off}}; k_{e0}) < C_{\text{thr}} \) where the blockade disappeared;
2. as type 1, but at the last assessment time a blockade was still present; and
3. there was no blockade at all assessment times.

Although this might seem counterintuitive, a type 3 observation does provide information, because no blockade occurs because \( C_{\text{thr}} \) is relatively high, \( V_e \) is large, and/or \( A \) is small. With only type 3 observations in the data set, only a lower limit of \( C_{\text{thr}} \) can be determined for a fixed \( k_{e0} \). Together with type 1 and type 2 observations, type 3 observations do allow for more accurate estimates of \( C_{\text{thr}} \) and \( k_{e0} \). Evidently, also the reverse is

Table 2. Solutions and Amounts of Local Anesthetics Administered in the Two Studies on Which the Current Analysis Is Based

<table>
<thead>
<tr>
<th>Study</th>
<th>Concentration, %</th>
<th>Amount, ml</th>
<th>Dose, mg</th>
<th>Labeled LA Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levobupivacaine</td>
<td>0.75</td>
<td>18</td>
<td>126</td>
<td>23</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>1</td>
<td>15</td>
<td>125</td>
<td>20</td>
</tr>
</tbody>
</table>

The local anesthetics (LAs) were administered as short infusions: the unlabeled LAs epidurally, the deuterium-labeled LAs intravenously.
true: When type 3 observations would be discarded, estimates of $C_{\text{thr}}$ would be biased downward.

**Main Assumptions.** According to the pharmacodynamic model, each segment is described by the following six parameters: $F_1$, $F_2$, $k_{a1}$, $k_{a2}$, $k_{e0}$, and $C_{\text{thr}}$. In addition, rate constants should be defined that describe the transport of the anesthetic between segments. However, there were at most only two informative observations per dermatome, and the pharmacokinetic analysis provides global rather than local absorption process parameters. So there are more parameters than observations. The following assumptions allowed us to proceed (fig. 1):

1. The longitudinal spread of the anesthetic solution across the segments of the epidural space occurs instantaneously.
2. The parameters $F_1$, $F_2$, $k_{a1}$, and $k_{a2}$ are equal for each segment, albeit that $F_1$ and $F_2$ are interpreted with respect to the fraction of the dose that is present in each segment after the initial spread.

Under these assumptions, both the local (segmental) and global (total epidural; obtained by adding all local absorption profiles) processes are described by the same parameters as those obtained from the pharmacokinetic analysis. If the local absorption or transport processes would be subject to large intrasegmental variability, it is unlikely that the global absorption profile would display such a clear biphasic pattern. Furthermore, distribution *via* the cerebrospinal fluid can be assumed to be minimal. We therefore believe that the postulated assumptions are reasonable.

After the initial spread, the amounts ($A_i$) of anesthetic present in each of the segments, and the central absorption volumes ($V_0$) at those segments, are not simultaneously identifiable. Only a combination parameter $A_{\text{thr}} = C_{\text{thr}} \cdot V_0 / A$ can be estimated. For parameter estimation, we therefore used (cf. equations 1 and 3):

$$A_i(t; k_{e0}) = \frac{F_1 \cdot k_{e0}}{k_{e0} - k_{a1}} \cdot (\exp(-k_{a1} \cdot t) - \exp(-k_{e0} \cdot t)) + \frac{F_2 \cdot k_{e0}}{k_{e0} - k_{a2}} \cdot (\exp(-k_{a2} \cdot t) - \exp(-k_{e0} \cdot t))$$

and assumed that a blockade occurs when $A_i(t; k_{e0}) \geq A_{\text{thr}}$. Parameter $A_{\text{thr}}$ is a measure of the anesthetic sensitivity. With two observations per dermatome, the remaining unknown parameter, $k_{e0}$, can be estimated. Parameters $A_{\text{thr}}$ and $k_{e0}$ were assumed to be lognormally distributed across the population. Because of the assumptions postulated, they can be estimated for each of the segments independently. Further details are given in the appendix.
Covariate Analysis
The pharmacokinetic and pharmacodynamic parameters (θ, indexed by i) were multiplied by factors containing log-transformed and centered (at 50) covariate age:

\[ \theta_i = \theta_{\text{pop},i} \cdot \exp(\alpha_{\text{AGE},i} \cdot c + \eta_i), \] (5)
where \( \theta_{\text{pop},i} \) denote population (typical) values; \( c = \log(\text{age}/50) \), \( \alpha_{\text{AGE},i} \) denote covariate coefficients; and \( \eta_i \) denote residual interindividual variabilities.

Statistical Analysis
Statistical analysis of the pharmacokinetic data were performed with the NONMEM version VI software package (a data analysis program for nonlinear mixed effects modeling) using its routine ADVAN11 for three-compartmental models of the intravenous data and analytical expressions (for processor time reduction) in $PRED$ for the five-compartmental model of the epidural data. Nonzero variance terms of the没事 were determined for the population model without covariate age; the structure was assumed to be the same for the model with the covariate included (mainly a decrease in variances is to be expected). Constant relative errors were assumed for the concentration measurements. All numerical results are given with three significant digits (conform NONMEM output). The empirical bayesian estimates (provided by NONMEM) of the disposition parameters were used for the estimation of the absorption parameters; the empirical bayesian estimates of the absorption parameters were used for the estimation of the pharmacodynamic parameters.

Statistical analysis of the pharmacodynamic data was performed using software written in the computer language C by one of the authors (E.O.) using the free GNU Scientific Library (GSL). Additional information regarding this is available on the Anesthesiology Web site at http://www.anesthesiology.org. With distributions of parameters \( A_{\text{thr}} \) and \( k_e0 \) postulated, the probability of observing the data per dermatome can be computed by integration across the \( (A_{\text{thr}}, k_e0) \) plane where it is possible that the data are as observed. The likelihood of observing the data are the product of the probabilities of all observations per dermatome. By maximizing this likelihood, the parameters of the lognormal distributions of \( A_{\text{thr}} \) and \( k_e0 \) can be obtained. (Note that NONMEM cannot be used when the integrand used for integration across the \( (A_{\text{thr}}, k_e0) \) plane is not continuous.) The boundaries of the 95% confidence intervals of the parameter estimates were determined by those parameter values that increase the objective function by 3.84 points (i.e., the likelihood profile method). Further details are given in the appendix.

The improvement of the model fit by inclusion of separate parameters for the different anesthetics and covariate age via forward selection was based on Akaike’s Information-Theoretic Criterion (AIC). The best model was defined as the one with the lowest value of the criterion, where AIC = MVOF + 2p, where MVOF is the \(-2\) log-likelihood and \( p \) is the number of parameters. The model with the lowest value of the criterion is assumed to have the best predictive properties. However, to present a classic measure of the significance of difference from zero of each of the final covariate coefficients of the pharmacokinetic models, likelihood ratio tests were performed (\( \Delta \) objective function value \( > 3.84 \) corresponds to \( P < 0.05; \Delta \) objective function value \( > 6.63 \) corresponds to \( P < 0.01 \)). To present a classic measure of significance of the selected covariate coefficients of the pharmacodynamic models, their 95% confidence intervals were graphically displayed together with zero ordinate lines.

Except for \( F_1 \), lognormal distributions were postulated for all parameters. The value of \( F_1 \) was constrained between 0 and 1, which was accomplished by using the inverse logit transformation on its \( \eta \). With distributions of \( A_{\text{thr}} \) and \( k_e0 \) available, the probability of blockade at each segmental level can be determined as a function of time and age. Blockade probabilities were computed with respect to a standardized dose of 100 mg for ropivacaine and 125 mg for levobupivacaine.

Results
Pharmacokinetic Analysis
Best, median, and worst model fits of the labeled local anesthetic concentration data (panels 1, 2, and 3, respectively) according to the coefficient of determination, together with the corresponding model fits of the unlabeled local anesthetic concentration data, are shown in figure 2. The worst model fits of the unlabeled local anesthetic data still provide adequate inputs for the pharmacodynamic models.

Levobupivacaine and ropivacaine disposition parameter estimates are presented in table 3. The only parameter that differed significantly between the two anesthetics was \( k_{31} \). A significant effect of age on \( V_1 \), and therefore on elimination clearance, was detected. In addition, a significant effect of age on intercompartmental distribution rate constant \( k_{12} \) was detected.

Levobupivacaine and ropivacaine absorption parameter estimates are presented in table 4. Parameters \( t_{0.5,a1} \) and \( t_{0.5,a2} \) were significantly different between the two anesthetics. Significant effects of age on \( t_{0.5,a1} \) and \( F_1 \) were detected. Parameter \( F \) was approximately 10% higher than 1 for both anesthetics (and had small interindividual variability around it).
Pharmacodynamic Analysis

Figure 3 presents the population estimates of $t_{1/2}$, $k_{e0}$ (converted from the $k_{e0}$ values for convenience of interpretation) and $A_{\text{thr}}$ with their 95% confidence intervals for each segment separately. Both parameters were significantly different between levobupivacaine and ropivacaine. At the L2 segment level, parameter $t_{1/2}$, $k_{e0}$ was approximately 5 min for levobupivacaine and 9 min for ropivacaine, which approximately doubled at higher and tripled at lower dermatome levels. Parameter $A_{\text{thr}}$ increased from S5 to T5, with the highest overall level for levobupivacaine. The variabilities in $k_{e0}$ and $A_{\text{thr}}$ were approximately 45% and 25%, respectively (data not shown).

Figure 4 presents the effects of age on the population values. For levobupivacaine, age increase the equilibration rate constants $k_{e0}$ at all segments. For ropivacaine, age increased the anesthetic sensitivity $A_{\text{thr}}$ at segments T12 and higher.

The nature of the pharmacodynamic data are such that the model fits exactly for each individual and dermatome (with two measurements (onset and offset of effect), and two parameters ($t_{1/2}, k_{e0}$ and $A_{\text{thr}}$)); only their probability distributions across the population can be estimated. The probabilities of blockade (after a dose of 100 mg ropivacaine and 125 mg levobupivacaine) as a function of time and age of the patient are presented in figure 5. The effects of increasing age are clearly visible at the higher segments (T9 and higher) where the probability of block dramatically increases, and by the increase of duration of block. To facilitate the interpretation of figure 5, a three-dimensional view of the blockade probabilities for levobupivacaine in a patient aged 50 yr is given in figure 6. Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

Discussion

We developed a predictive population PK-PD model of epidural anesthesia and determined its parameters, taking into account the effects of age, for the local anesthetics levobupivacaine and ropivacaine. The pharmacokinetic analysis yielded similar population parameter estimates with respect to our previous stud-

Table 3. Disposition Pharmacokinetic Model Parameter Estimates for Levobupivacaine and Ropivacaine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>SE</th>
<th>$\omega_i^2$</th>
<th>SE</th>
<th>$\sigma_{\text{AGE}}$</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$</td>
<td>6.85</td>
<td>0.404</td>
<td>0.0352</td>
<td>0.00973</td>
<td>-0.193$^*$</td>
<td>0.0949</td>
</tr>
<tr>
<td>$k_{10}$</td>
<td>0.0522</td>
<td>0.00352</td>
<td>0.0724</td>
<td>0.0315</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{12}$</td>
<td>0.152</td>
<td>0.0183</td>
<td>0.0357</td>
<td>0.0188</td>
<td>0.579$^\dagger$</td>
<td>0.155</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>0.0884</td>
<td>0.00670</td>
<td>0.0241</td>
<td>0.0111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>0.0519</td>
<td>0.00508</td>
<td>0.147</td>
<td>0.0399</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{31,\text{levo}}$</td>
<td>0.00732$^\ddagger$</td>
<td>0.000563</td>
<td>0.1469</td>
<td>0.0185</td>
<td>-0.213</td>
<td>0.137</td>
</tr>
<tr>
<td>$k_{31,\text{ropi}}$</td>
<td>0.0137$^\ddagger$</td>
<td>0.000782</td>
<td>0.0213</td>
<td>0.0185</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.00991</td>
<td>0.000904</td>
<td>0.0213</td>
<td>0.137</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^*$ $P < 0.05$, $^\dagger P < 0.01$, $^\ddagger P < 0.01$ between anesthetics.

$k_i$ = rate constant between compartments $i$ and $j$; $V_1$ = volume of central compartment; $\omega_i^2$ = variance of first-level random effect; $\sigma^2$ = variance of second-level random effect.
ies. The PK-PD model was able to predict the probability of block and duration of anesthesia per segment. The covariate analysis showed that age had a significant and clinically important effect on the spread and duration of analgesia.

We previously determined absorption kinetics after epidural administration of bupivacaine, levobupivacaine, and ropivacaine. Stable isotope-labeled analogs were intravenously infused to obtain disposition kinetics. Subsequently, with the use of the disposition kinetics and the plasma concentration of the epidurally administered unlabeled local anesthetic, the absorption kinetics could be obtained by deconvolution. The plasma concentration-time curves of individual patients were adequately described by fitting directly the aggregated model of two parallel first-order absorption compartments and the disposition profile (a two- or three-compartmental model). These analyses allowed the determination of the profiles of the different local anesthetics and the effects of age. However, these individual analyses may be hampered by interindividual variability, caused by sex differences and genetic, environmental, and pathophysiologic factors. A population approach of these data may be attractive because it can explain a part of the wide variability by incorporating covariates, such as the type of local anesthetic and age. In addition, it enables the development of models that are able to

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>SE</th>
<th>$\omega^2$</th>
<th>SE</th>
<th>$\sigma_{AGE}$</th>
<th>SE</th>
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</thead>
<tbody>
<tr>
<td>$t_{1/2,a1,levo}$</td>
<td>5.76‡</td>
<td>0.466</td>
<td>0.147</td>
<td>0.0281</td>
<td>-0.666†</td>
<td>0.129</td>
</tr>
<tr>
<td>$t_{1/2,a1,ropi}$</td>
<td>9.66‡</td>
<td>0.837</td>
<td>0.0783</td>
<td>0.0150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2,a2,levo}$</td>
<td>425‡</td>
<td>27.4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$F_{1,levo}$</td>
<td>0.193</td>
<td>0.0112</td>
<td>0.127</td>
<td>0.0338</td>
<td>-0.337*</td>
<td>0.142</td>
</tr>
<tr>
<td>$F_{1,ropi}$</td>
<td>0.221</td>
<td>0.0134</td>
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<td>$\sigma^2$</td>
<td>0.0149</td>
<td>0.00141</td>
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* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.01$ between anesthetics.

$F$ = total fraction absorbed; $F_1$ = fraction absorbed in compartment 1; $t_{1/2,a1}$ and $t_{1/2,a2}$ = absorption half-lives (see text); $\omega^2$ = variance of first-level random effect; $\sigma^2$ = variance of second-level random effect.

Fig. 3. Equilibration half-lives and absorption thresholds, with their 95% confidence intervals, at segments S5–T5 of the two local anesthetics under study. To guide the eye, dashed lines were drawn at the parameter values at level L2 (epidural injection was at the L3–L4 interspace).
make predictions about certain clinically important endpoints, such as maximal level and duration of blockade. This may, consequently, improve therapeutic outcome in future patients.6

**Pharmacokinetic Analysis**

The current analysis yielded similar results with respect to our previous studies; small differences, however, were apparent. For example, we now observed that the clearances of the two anesthetics decrease significantly with increasing age.

The observed differences between the absorption parameters of the two anesthetics can be explained from their vasoconstrictory and vasodilatory properties.5 The effects of those differences on the concentration in the epidural space after a standardized bolus dose are shown in figure 7. LevoBupivacaine concentration levels are the highest, and this anesthetic could be called the most efficient in terms of concentration. This observation has to be linked to the pharmacodynamic potency to determine whether it is also effect efficient (see Discussion, Pharmacodynamic Analysis section).

Parameter $F$, which represents the fraction of the administered dose that is present in the patient’s blood, should be 1. It was greater than 1 for levobupivacaine and ropivacaine. Possible explanations are given in our previous articles3–5; in brief, bioavailability may be overestimated because of the finite experiment time from which the disposition kinetics (in particular elimination clearance) are determined.

**Pharmacodynamic Analysis**

We observed that the sensitivity to the two anesthetics, quantified by an increase of parameter $A_{th}$, decreased with segment height. Assuming that the sensitivity of the nerves to the presence of an anesthetic, and the volume of the central absorption compartments do no differ between segments, this decrease is due to a smaller amount of anesthetic reaching the higher segments. The overall $A_{th}$ is highest for levobupivacaine. So although the absorption charac-
acteristics cause this anesthetic to be concentration efficient, this is counteracted by its lower sensitivity (figs. 3 and 7). Ropivacaine was found to have a lower speed of onset and offset (as expressed by $t_{1/2,ke0}$) than levobupivacaine. This may be explained by the fact that the physiochemical properties of ropivacaine are similar to those of levobupivacaine, apart from its lower lipid solubility. Because lipid solubility is related to potency, ropivacaine may be less potent.17 The smaller $t_{1/2,ke0}$ in the neighborhood of the L2 segment is probably related to differences in the distribution of the anesthetics in the epidural space close to the site of injection.

Anatomical and physiologic changes associated with advancing age may affect the pharmacokinetics and the nerve block characteristics after epidural administration of local anesthetics. A declining number of neurons, deterioration in myelin sheaths in the dorsal and ventral roots, changes in the anatomy of the spine, and intervertebral foramina may contribute to altered nerve block characteristics after epidural anesthesia.18,19 Furthermore, the number of axons in peripheral nerves decreases with advancing age, and the conduction velocity diminishes, particularly in motor nerves.19–21 With increasing age, changes in the connective tissue ground substances and epidural fat may result in changes in local distribution, i.e., in the distribution rate of the local anesthetic from the site of injection (the epidural space) to the sites of action.18

We observed important age effects for ropivacaine and levobupivacaine, respectively: (1) $A_{th}$ decreased at the higher segment levels (T12 and higher); and (2) onset and offset of the sensory blockade, as expressed by parameter $t_{1/2,ke0}$, was faster with increased age. The most probable mechanism of an increased anesthetic sensitivity with age is an age-dependent change in the longitudinal spread of the anesthetics in the epidural space. This is evident because we observed an increased sensitivity with age mainly at the higher segments. The reduced loss of anesthetic via sclerotic intervertebral foramina during its rostral spread with increasing age may explain this observed age effect. The higher level of analgesia in older patients may as well be attributed to a greater sensitivity (a lower $A_{th}$).
such that with the same local anesthetic concentrations at higher thoracic segments, blockade occurs in older but not in younger patients. Consequently, to obtain comparable epidural blocks, smaller doses of local anesthetic solutions should be administered to older as compared with younger patients. The effect of age on the speed of onset and offset of effect is probably related to changes in epidural fat. Uptake into extraneural tissues, such as epidural fat, limits the rate and extent of drug distribution to the nerves and thereby changes the time profile of clinical potency.22

PK-PD Models of Spinal Anesthesia

To the best of our knowledge, this is the first PK-PD model developed for lumbar epidural administration of local anesthetics. There are, however, PK-PD models for spinal anesthesia in pigs and in humans.7,23,24 Shafer et al.25 performed PK-PD modeling of intrathecal neostigmine using cerebrospinal fluid samples and analgesia (visual analog scale) scores. The pharmacokinetic part of their model included a component to account for the spatial dimension in the intrathecal administration–analgesia relation. The pharmacokinetic model developed by Ummenhofer et al.24 consists of four spatially interconnected subunits of four serially connected compartments to describe drug distribution in each subunit. From microdialysis data, it was not possible to estimate all model parameters for all subunits, and some additional assumptions had to be made. For example, exchange between spinal levels was assumed to occur only via the cerebrospinal fluid and not via the epidural space. For our model of epidural anesthesia, we assumed that no exchange occurs via the cerebrospinal fluid and epidural space, except in the latter during epidural administration. Schnider et al.7 developed a population pharmacodynamic model of spinal anesthesia from pinprick assessments. Although their model is applicable to epidural anesthesia, it is unable to predict sensory blockade at levels lower than the maximum. Furthermore, because they did not take into account pharmacokinetic data (on disposition and absorption) and hence the local anesthetic concentration, their pharmacodynamic analysis is affected by pharmacokinetic variability. Although this seems of limited importance when treating and predicting epidural anesthesia in a new patient, the inclusion of covariates in the pharmacokinetic model will improve the prediction of sensory anesthesia in this particular patient.

Critique on Methods

A potential drawback of our model is the underlying essential assumption that rostral and caudal spread of the anesthetic in the epidural space is instantaneous and subsequently remains unchanged (apart from absorption). In reality, the local anesthetic spreads with a certain delay. Incorporation of segment-dependent delay is not feasible, because we have only two measurements per dermatome (onset and offset times of blockade). Note that in reality t12/2t is not the delay to the segments but the delay from the segment to the effect site (i.e., the spinal nerve roots). Consequently, we may have slightly overestimated the value of t12/2t.

Furthermore, the results that we present here are valid for the specific volume of the local anesthetic given as well as the location of the epidural puncture (L3–L4 interspace). It has been shown that in contrast to dose, volume per se has little or no effect on sensory block height and quality of anesthesia.25,26 We expect, however, that the site of injection affects the parameter values of our model.

The way covariate age was included in the models allows for a covariate effect in one way only (either a decrease or an increase). In our previous articles, patients were assigned to age groups; however, this allowed for physiologically unrealistic covariate effects.

There was no intraindividual variability in the pharmacodynamic data because of the nature of the binary assessments. There was, however, intraindividual uncertainty in the actual times of onset and offset of effect, depending on the sampling times according to the protocol; this uncertainty will bias the estimates of interindividual variability (ωa0 and ωe0) upward.

Conclusions

In conclusion, we developed a predictive PK-PD model of epidural anesthesia in humans. We were able to demonstrate the importance of age on the spread of the sensory blockade as well as on the speed of onset/offset of blockade. The model allows the study of various important factors in epidural anesthesia, such as the site of injection, the volume of the injected fluid, combined spinal–epidural injections, anesthetic-opioid interaction, and pregnancy. Furthermore, the model may be used in the development and study of new local anesthetics for epidural use.

References


Anesthesiology, V 109, No 4, Oct 2008

Appendix

**Likelihood Function for the Set of Observations**

For a type 1 observation, pinpoint assessment times yield intervals (on,1, off,1) and (on,2, off,2) that constitute the closest intervals around the actual onset and offset times of effect (fig. 8). The remaining assessments do not contain any additional information, because they were always 0 for t ≤ on,1 and t ≥ off,2, and 1 for t ≤ off,1 (a result of the choice of assessment times with respect to the rate of change in the effect site absorption profile). Therefore, the uncertainty about whether there is a blockade can be estimated and has to be neglected, but there is uncertainty with respect to the actual onset and offset times. This uncertainty is taken into account by the postulated normal probability distributions for the logarithms of A thr and kco with variances ω2 thr and ω2 kco respectively. Thus, they are a measure of the combination of intra-individual and interindividual variabilities (which cannot be separated). Figure 9 depicts the (A thr, kco) area for which it is possible that the observed intervals (on,1, off,1) and (on,2, off,2) are observed. The likelihood of an observation in individual t is given by

\[
\mathcal{L}_{t} = \int_{t_{on1}}^{t_{off1}} \int_{t_{on2}}^{t_{off2}} N_{t}(A_{thr}; a_{thr}, \omega_{thr}^2) N_{t}(k_{co}; a_{co}, \omega_{co}^2) dA_{thr} dk_{co}
\]

(6)

where N t denotes the fact that A thr and k co are normally distributed in the logdomain and μ and σ denote, in NONMEM parlance, typical population values and variabilities. The integration interval for A thr depends on k co, and the integration interval for k co is determined by nonempty A thr integration intervals (fig. 9). The integrals are evaluated in the logdomain; the inner integral can be numerically approximated by one of the GSL gsl_cdf_normal routines, and the outer integral can be numerically approximated by one of the GSL gsl_integration_qag routines, depending on whether the k co range is finite or infinite. The likelihood of the set of observations is given by the product of equation 7 for each individual.

For a type 2 observation, a blockade is still present at the last assessment time, so A t (off,2) = A t (off,1) = A thr and t off,2 is not observed, which means that the information about A thr and k co is not bounded by the line A t (off,2) = k co in figure 9, and the area of integration therefore also includes the horizontally shaded part (with k co = 0).

For a type 3 observation, A t (off,1) < A thr for all t ≥ t max (the observations are not independent, and function A (t) has only one maximum).
The implementation of the integrals in the C program were checked using Monte Carlo simulation, i.e., by counting the number of samples from the lognormal distributions of $A_{\text{thr}}$ and $k_{\text{eo}}$ that fall within the region of integration.

The model parameters were estimated by the method of maximum likelihood, i.e., they are given by those values that maximize $L = \prod L_i$ (for all individuals $i$, equation 6); the maximum was numerically determined by the GSL routine gsl_multimin_fminimizer_nmsimplex.

**Initial Parameter Values**
Suppose that $t_{\text{on},1} = t_{\text{on},2}$ and $t_{\text{off},1} \sim t_{\text{off},2}$, so that they can be approximated by their averages $t_{\text{on}}$ and $t_{\text{off}}$. Then there exists a unique relation between $(t_{\text{on}}, t_{\text{off}})$ and $(A_{\text{thr}}, k_{\text{eo}})$, the latter are given by those values that satisfy $A_e(t_{\text{on}}; k_{\text{eo}}) = A_{\text{thr}}$, and $A_e(t_{\text{off}}; k_{\text{eo}}) = A_{\text{thr}}$ (using equation 4). They are unique because $A_e(t_{\text{on}}; k_{\text{eo}})$ increases while $A_e(t_{\text{off}}; k_{\text{eo}})$ decreases when $k_{\text{eo}}$ increases. The equality is numerically found by the GSL root-finding routine gsl_root_fsolver_brent. Initial parameter values were calculated as the means and variances of the logarithms of the $A_{\text{thr}}$ and $k_{\text{eo}}$ estimates at each dermatome for all individuals from the type 1 observations.

**Blockade Probabilities**
Once the distributions of $A_{\text{thr}}$ and $k_{\text{eo}}$ are known (their parameters estimated), the probability of blockade at time $t$ is given by:

$$
P \{ \text{blockade at } t \} = P \{ A_e(t; k_{\text{eo}}) \geq A_{\text{thr}} \}$$

$$= \int_0^\infty \int_0^\infty e^{-(\mu_A + \sigma_A^2)} N_t(A_{\text{thr}}; \mu_A, \sigma_A^2) N_t(k_{\text{eo}}; \mu_{k_{\text{eo}}}, \sigma_{k_{\text{eo}}}) dA_{\text{thr}} dk_{\text{eo}}$$

where the population values $\mu_{A_{\text{thr}}}$ and $\mu_{k_{\text{eo}}}$ are functions of age as given by equation 5, and the parameters of $A_e(t; k_{\text{eo}})$ (equation 4) are given by population estimates of $F_1$, $F_2$, $k_{a1}$, and $k_{a2}$, which are also functions of age. When the population distributions of the absorption parameters are postulated correctly and/or their variances are small, the bias caused by taking their population estimates instead of in addition integrating across their respective distributions is assumed to be negligible.
Are epidurals worthwhile in vascular surgery?
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Introduction

Major vascular surgery is considered to be a high-risk procedure. It is often applied in elderly patients, who exhibit many comorbidities such as ischaemic heart disease, renal insufficiency and diabetes. Many of these patients are at increased risk for perioperative complications. Consequently, these patients would benefit from anaesthetic techniques reducing those risks. The question whether epidural or general anaesthesia is preferable for vascular surgery has been debated for years.

The present review will focus on the probable advantages of epidural anaesthesia for vascular surgery.

Physiologic effects

The use of epidural anaesthesia provides physiologic benefits and may attenuate the pathophysiology that occurs following surgery. This may be associated with a reduction in perioperative mortality and morbidity when compared with general anaesthesia.

Thoracic epidural anaesthesia (TEA) covering the cardiac segments (T1–T4) improves an ischaemia-induced left ventricular dysfunction; reduces electrocardiographic, echocardiographic and angiographic signs of coronary insufficiency; decreases the incidence of arrhythmias and provides relief of ischaemic chest pain [1]. Local anaesthetics have the capability to block afferent and efferent signals to and from the spinal cord, thus suppressing the surgical stress response [2]. Major surgery is associated with a hypercoagulable state that persists into the postoperative period. The incidence of thromboembolic complications is lower in patients operated upon under epidural anaesthesia compared to those given general anaesthesia [3]. Modulation of the surgically induced changes in coagulation or fibrinolysis by epidural anaesthesia might be due to an increased blood flow with subsequent reduced venous stasis, to effects of the local anaesthetics themselves and to blunting the stress response [3,4].

Epidural anaesthesia extending above T12 is associated with splanchnic sympathetic nervous blockade, resulting in reduced inhibitory gastrointestinal tone and increased intestinal blood flow. Perioperative intestinal hypoperfusion is a major contributing factor leading to organ dysfunction. TEA during and after major surgery has been shown to protect the gut from decreased microvascular perfusion and to improve the mucosal blood flow, even under conditions of decreased perfusion pressure [5,6].

TEA with postoperative thoracic epidural analgesia has been shown to shorten the time to first bowel movement [7] and the duration of postoperative colonic ileus [8].

Vascular surgery

Various comorbidities associated with advanced age, such as ischaemic heart disease, renal insufficiency and diabetes are robust, predictors of cardiac complications in
Are epidurals worthwhile in vascular surgery? Veering 617

Aortic surgery

Major vascular surgical procedures are amenable to epidural anaesthesia combined with general anaesthesia (EA + GA). Aortic cross clamping and unclamping are associated with complex cardiovascular, renal, humoral and haemostatic changes [11]. During reconstructive aortic surgery, clamping and unclamping is usually well tolerated but may produce severe haemodynamic disturbances.

Patients with TEA + GA to have a more stable haemodynamic course during the critical times of aortic clamping and unclamping with fewer fluctuations in blood pressure and heart rate [12,13].

With cross clamping both with epidural anaesthesia + general anaesthesia and with general anaesthesia alone, signs of myocardial ischaemia did occur. So the favourable factor of epidural anaesthesia on the myocardial oxygen supply–demand relationship did not influence the incidence of intraoperative myocardial ischaemia [14].

Discrepancies exist between studies that have evaluated the effect of epidural anaesthesia + general anaesthesia and postoperative analgesia in comparison with general anaesthesia and postoperative systemic opioid-based pain relief on the postoperative cardiac outcome in patients who underwent elective abdominal aortic surgery. Some studies [15,16] involving high-risk (e.g. aortic reconstruction) surgery patients have reported significant reductions in cardiac morbidity associated with the use of intraoperative and postoperative epidural anaesthesia/analgesia using local anaesthetics and opioids.

Others [13,17–19] did not demonstrate a decrease in cardiac morbidity in patients undergoing aortic reconstructions treated with intraoperative TEA + light general anaesthesia. However, epidural anaesthesia and analgesia was associated with shortened intubation times and ICU stay.

A meta-analysis of 17 studies examining the effect of postoperative epidural analgesia on postoperative cardiac morbidity showed a significant reduction in postoperative myocardial infarction in the epidural group continued for more than 24 hours [20]. Patients underwent abdominal and vascular surgery and had a history of preoperative cardiac morbidity. Subgroup analysis demonstrated that thoracic epidural analgesia was superior to lumbar epidural analgesia in reducing postoperative myocardial infarction. These findings suggest that thoracic epidural anaesthesia may have a favorable effect on cardiac morbidity, however more randomized clinical trials are warranted.

A part of postoperative complications is caused by respiratory problems during the early postoperative recovery period. A meta-analysis by Ballantyne et al. [21] found that postoperative epidural analgesia was associated with a decrease in the incidence of atelectasis, pneumonia, overall pulmonary complications and an increase in the arterial partial pressure of oxygen, compared with systemic opioid administration. These findings suggest that postoperative epidural analgesia has a beneficial effect on pulmonary morbidity.

A recent systemic review showed that epidural analgesia provides better pain relief and reduces the duration of tracheal intubation after open abdominal aortic surgery compared to systemic opioid-based relief [22]. These findings suggest that epidural pain relief may be advantageous for pulmonary patients undergoing abdominal aortic surgery.

Peripheral vascular surgery

Studies of Christopherson et al. [23] and of Bode et al. [24] reported no difference in myocardial ischaemia, major cardiac morbidity or operative mortality when comparing epidural anaesthesia and analgesia with general anaesthesia followed by intravenous patient-controlled analgesia (PCA) in patients undergoing lower extremity vascular surgery. The limitation of both studies was that they were inadequately powered to detect differences between anaesthetic techniques. However, a benefit of epidural anaesthesia over general anaesthesia was a reduction in the incidence of graft occlusion [4,15,25].

Lower extremity revascularization is performed in patients with a high incidence of coexistent diseases. Krupski et al. [26,27] compared the difference in early and late cardiac morbidity in patients undergoing suprainguinal aortic operations versus patients undergoing infrainguinal vascular operations. The incidence of early postoperative cardiac complications was the same in both groups, however cardiac morbidity rates at 2 years were greater for infrainguinal versus abdominal aortic procedures. This may be due to a greater prevalence of diabetes and cardiac morbidities in patients with peripheral vascular diseases. In both studies the effect of anaesthetic technique on cardiac morbidity was not investigated.

The major drawbacks of early prospective studies are methodological flaws, including different regimens of epidural anaesthesia, different protocols of postoperative pain treatment, inclusion of small numbers of patients and possible investigator bias.

the vascular patient [9]. Cardiac and pulmonary complications remain the main causes of perioperative morbidity associated with major vascular surgery [10].

A commonly asked question is whether the mentioned physiologic benefits ascribed to epidural anaesthesia will make a difference in the outcome of vascular surgical patients.

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In order to avoid those deficiencies of design and methodology Norris et al. [28] performed a double-masked randomized controlled trial of 168 patients undergoing abdominal aortic surgery. In this study strict intraoperative and postoperative protocols were used to guide and optimize perioperative management and postoperative analgesia. Participants were allocated into four treatment groups, two groups received TEA combined with a light GA followed by either PCA or epidural patient-controlled analgesia (EPCA) and two groups received GA alone followed by either PCA or EPCA.

The primary outcome was length of stay; secondary outcomes included selected postoperative morbidities like pulmonary complications and cardiovascular events. Cardiac morbidity was defined as myocardial infarction, angina, congestive heart failure and ventricular tachyarhythmia. Postoperative outcomes were not influenced by intraoperative and postoperative anesthetic regimens. This implies probably that perioperative care of patients undergoing vascular procedures seems to be important regardless of the anesthetic techniques used [29].

**Conclusion**

Existing studies fail to demonstrate improved clinical outcome and reduced mortality for epidural anaesthesia or combined epidural/general techniques compared with general anaesthesia. Large, well designed randomized clinical trials on a long-term basis are necessary to draw solid conclusions on the effect of anesthetic techniques on eventual outcome after vascular surgery.

However it seems more reasonable that the real aim should be to improve the perioperative care of vascular surgery patients rather than to focus on the effect of the particular anesthetic technique on patient outcome following vascular surgery.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


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Failed spinal anaesthesia: mechanisms, management, and prevention

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Although spinal (subarachnoid or intrathecal) anaesthesia is generally regarded as one of the most reliable types of regional block methods, the possibility of failure has long been recognized. Dealing with a spinal anaesthetic which is in some way inadequate can be very difficult; so, the technique must be performed in a way which minimizes the risk of regional block. Thus, practitioners must be aware of all the possible mechanisms of failure so that, where possible, these mechanisms can be avoided. This review has considered the mechanisms in a sequential way: problems with lumbar puncture; errors in the preparation and injection of solutions; inadequate spreading of drugs through cerebrospinal fluid; failure of drug action on nervous tissue; and difficulties more related to patient management than the actual block. Techniques for minimizing the possibility of failure are discussed, all of them requiring, in essence, close attention to detail. Options for managing an inadequate block include repeating the injection, manipulation of the patient’s posture to encourage wider spread of the injected solution, supplementation with local anaesthetic infiltration by the surgeon, use of systemic sedation or analgesic drugs, and recourse to general anaesthesia. Follow-up procedures must include full documentation of what happened, the provision of an explanation to the patient and, if indicated by events, detailed investigation.

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Two conditions are, therefore, absolutely necessary to produce spinal anesthesia: puncture of the dura mater and subarachnoid injection of an anesthetic agent.

Gaston Labat, 1922

Spinal (intrathecal) anaesthesia is generally regarded as one of the most reliable of regional block methods: the needle insertion technique is relatively straightforward, with cerebrospinal fluid (CSF) providing both a clear indication of successful needle placement and a medium through which local anaesthetic solution usually spreads readily. However, the possibility of failure has long been recognized, the above quote being taken from the work of Gaston Labat,24 the ‘father’ of modern regional anaesthesia. His two conditions for success, although perhaps a little simplistic when related to current knowledge, still indicate the essence of the method and provide a starting point for the consideration of failure, although it may be helpful to define exactly what this means first. Literally, the word failure implies that a spinal anaesthetic was attempted, but that no block resulted; this happens, but perhaps a commoner outcome is that a block results, but is inadequate for the proposed surgery. Such inadequacy may relate to three components of the block: the extent, quality, or duration of local anaesthetic action, often with more than one of these being inadequate. This review has considered all three eventualities within the definition of ‘failure’.

Most experienced practitioners would consider the incidence of failure with spinal anaesthesia to be extremely low, perhaps less than 1%. However, a figure as high as 17% has been quoted from an American teaching hospital, yet most of the failures were judged to be ‘avoidable’.28 A survey at another such institution considered that this high rate was ‘unacceptable’, and recorded the much lower, but still significant, figure of 4%, with ‘errors of judgement’ as the major factor.32 The clear implication is that careful attention to detail is vital, and it has been shown that a failure rate of <1% is attainable in everyday practice.17 Minimizing the incidence of failure is obviously a pre-requisite for gaining the benefits of spinal anaesthesia, and prevention must start with full recognition of the potential pitfalls so that clinical practice can be tailored to their avoidance.
In general terms, block failure is usually ascribed to one of three aspects: clinical technique, inexperience (of the unsupervised trainee especially), and failure to appreciate the need for a meticulous approach. However, such broad categories reveal little about the many detailed ways in which an intrathecal injection can go astray within each of the five phases of an individual spinal anaesthetic, these being, in sequence, lumbar puncture, solution injection, spreading of drug through CSF, drug action on the spinal nerve roots and cord, and subsequent patient management. All of the problems involved are well described in the literature, but usually long ago, and many practitioners seem unaware of the issues involved. For instance, the neuroscience division of AstraZeneca received 562 ‘Product Defect Notification’ reports in the 6 yr to December 31, 2007, all ascribing failed spinal anaesthetics to ineffective bupivacaine solution (Fig. 1). Nearly one-third of reports (179) were from the UK, but virtually every country where the drug is marketed was represented. However, analysis showed that the returned material was within the product’s specification in every case so a formal review, based on a literature search, was thought to be worthwhile.

**Search strategy**

For this review ‘PubMed’ and ‘Google’ databases were searched using the terms ‘failed regional anaesthesia’, ‘failed regional anesthesia’, ‘failed spinal anaesthesia’, and ‘failed spinal anesthesia’. Relevant articles were retrieved as were any possibly relevant papers in their reference lists. Supporting searches were performed on subjects that may not have been otherwise identified, specific examples being CSF volume, dural ectasia, and the chemical compatibility of local anaesthetics with adjuncts.

In addition, searches were made using ‘Planet’ (an AstraZeneca internal database), ‘Biosis’, ‘Current Contents’, ‘Embase’, ‘PsycINFO’, ‘Medline’, and ‘Medline Daily update’, using the terms ‘Failed Spinal Anaesthesia’ and ‘Failed Spinal Anaesthesia’ as sole search terms and ‘spinal anesthesia’ or ‘spinal anaesthesia’ or ‘spinal anesthetic’ or ‘spinal cord anaesthesia’ or ‘spinal cord anesthesia’ or ‘anaesthesia, spinal’ or ‘anaesthesia, spinal anesthesia, spinal’ and ‘treatment failure’ or ‘therapy failure’, and ‘Intrathecal’. All papers identified as relevant are included in this review.

**Mechanisms and their prevention**

*Failed lumbar puncture*

Inability to obtain CSF, sometimes referred to as a ‘dry tap’, is the only cause of failure which is immediately obvious. A needle with a lumen blocked at the outset is a theoretical possibility, but is most unlikely with modern equipment. However, both needle and stylet must be checked for correctness of fit before use, and the needle should not be advanced without the stylet in place because tissue or blood clot can easily obstruct the fine bore needles used now. Otherwise, a failed lumbar puncture is virtually always because of either poor positioning of the patient or incorrect needle insertion, both factors being within the control of the anaesthetist. Abnormalities of the spine (kyphosis, scoliosis, calcification of ligaments, consequences of osteoporosis), obesity, and patient anxiety make both positioning the patient and needle insertion more difficult, especially in the elderly. Texts of regional anaesthesia give more extensive instruction than can be provided here, and good clinical training is the key to success, but most difficulties are attributable to lack of adherence to the basic rules.

**Positioning**

The patient is placed on a firm surface; the lumbar laminae and spines are ‘separated’ maximally by flexing the whole spine (including the neck), the hips, and knees; rotation and lateral curvature of the spine are avoided; these points apply to lumbar puncture in both sitting and lateral horizontal positions; the former is usually an easier option in ‘difficult’ patients, but sometimes the reverse is true. The role of the assistant in achieving and maintaining the patient in the correct position cannot be underestimated.33

**Needle insertion**

Although its accurate identification can be difficult using clinical land-marks, what is judged to be the third lumbar inter-space is used usually, but examination may indicate that another is preferable. However, care should be taken not to venture too cephalad and risk damage to the spinal cord.33 With the midline approach, insertion should start precisely in the mid-line, mid-way between the posterior spines, with the needle shaft at right angles to the back in both planes. Small, incremental changes in needle angle...
should be made only if there is resistance to advancement; if resistance is met, cephalad angulation should be tried first, and such angulation may be appropriate from the start if the patient is unable to flex fully (e.g. the obstetric patient at term). A degree of caudal angulation is sometimes needed, with a slight lateral direction being required very rarely. All authorities recommend that the anaesthetist should have a good knowledge of spinal anatomy and relate these to changes in tissue resistance as the needle is advanced so that a mental ‘picture’ of where the needle tip lies is appreciated.

The above points apply specifically to the midline approach; lateral or paramedian approaches are preferred by some, especially if the mid-line ligaments are heavily calcified, but they are inherently more complex techniques. However, in the face of difficulty, the same basic rules apply: make sure that the patient is in the correct position and that the correct angles and insertion technique are used.

**Adjuncts**
A calm, relaxed patient is more likely to assume and maintain the correct position, so explanation (before and during the procedure) and gentle, unhurried patient handling are vital; light anxiolytic premedication contributes much to relaxing the patient; local anaesthetic infiltration at the puncture site must be effective without obscuring the landmarks, but must include both intradermal and s.c. injection. Achieving the correct position is a particular challenge in the patient in pain (e.g. from a fractured hip) and systemic analgesia (i.v. or inhalation) helps considerably. The aim of such adjuncts is to optimize the patient’s position and to prevent any movement. As will be discussed later, it takes only slight movement to displace the needle from its target.

Advances in ultrasound technology are reaching the stage where it can be used to overcome difficulties with lumbar puncture, but clinicians will still need to be aware of the problems and how they should be overcome.

**Pseudo-successful lumbar puncture**
The appearance of clear fluid at the needle hub is usually the final confirmation that the subarachnoid space has been entered. Rarely, however, the clear fluid is not CSF, but local anaesthetic injected as a ‘top-up’ for an epidural which then proved inadequate for a Caesarean section, or even spreading there from the lumbar plexus. Unfortunately, a positive test for glucose in the fluid does not confirm that this fluid is definitely CSF because extracellular fluid constituents diffuse rapidly into fluids injected into the epidural space. Another, even rarer, suggested cause of clear fluid appearing at the needle hub, but not confirming successful lumbar puncture, is a congenital arachnoid cyst.

**Solution injection errors**
The appearance of CSF in the needle hub is an essential pre-requisite for spinal anaesthesia, but it does not guarantee success, which also requires that a fully effective dose is both chosen and actually deposited in the CSF.

**Dose selection**
Studies of many factors influencing intrathecal drug spread have shown that the dose injected, within the range normally used, has only a small effect on the extent of a spinal anaesthetic, but is far more important in determining the quality and duration of block. Overall, the actual dose chosen will depend on the specific local anaesthetic used, the baricity of that solution, the patient’s subsequent posture, the type of block intended, and the anticipated duration of surgery. Thus, knowledge of the factors influencing intrathecal drug spread and clinical experience with any particular local anaesthetic preparation are important guides to choosing an effective dose.

However, the need to guarantee an adequate effect means that the doses of drugs injected in standard ‘single shot’ techniques are larger than is strictly necessary, experience with dose titration during continuous spinal anaesthesia showing clearly that lower doses are often effective. In attempts to either minimize hypotension, for example by attempting to produce a unilateral block, or speed postoperative mobilization, by decreasing duration, some practitioners use lower doses than is traditional (e.g. 5–10 rather than 15 mg of hyperbaric bupivacaine). Used correctly, and in appropriate situations, such doses can be reliable, but they do mean that the margin for error is reduced and that the consequences of other problems (e.g. Loss of injectate—see below) will be exaggerated and so risk an inadequate block. It becomes even more important to ensure that the whole of that lower dose reaches the CSF and then spreads properly, remembering that the ‘dead space’ of the needle will contain a significant proportion of what is a small volume to start with.

**Loss of injectate**
The Luer connection between syringe and needle provides a ready opportunity for leakage of solution. A particular variant of this problem being a leak through a defect at the junction of needle hub and shaft. Given the small volumes involved, the loss of even a few drops may cause a significant decrease in the mass of drug reaching the CSF, and thus in its effectiveness. To avoid this, it has long been conventional teaching that the syringe containing the injectate must be inserted very firmly into the hub of the needle, and that a subsequent check is made that no leakage occurs.

**Misplaced injection**
Needle and syringe must be connected firmly, but great care should be taken to avoid either anterior or posterior
displacement of the needle tip from subarachnoid to epidural space, where deposition of a spinal dose of local anaesthetic will have little or no effect. Fluid aspiration, after attachment of the syringe, should confirm free flow of CSF and, thus, that the needle tip is still in the correct space, but such aspiration may displace the tip unless performed carefully, as may the force of the injection of the syringe contents. To prevent displacement at any stage, it has been advocated that the dorsum of one hand should be anchored firmly against the patient’s back and the fingers used to immobilize the needle, while the other hand is used to manipulate the syringe. Most practitioners would recommend aspiration for CSF after the injection to confirm that correct placement is maintained, and some advocate that this is done half way through as well although neither of these practices has been shown to influence the outcome of the block.40 Tip displacement must be guarded against with any type of spinal needle, but it is a particular issue with the ‘pencil point’ needles now used widely to minimize the incidence of post-dural puncture headache. The opening at the end of these needles is proximal to the tip, so only a minor degree of ‘backward’ movement during syringe attachment may result in epidural injection as was recognized at an early stage in the widespread use of such needles. The distances involved are of the order of a millimetre or two, but (as with leakage) misplacement of only a small amount of solution can have significant effects. An additional issue with pencil-point needles is that the opening, being much longer than the bevel of a Quincke needle, may ‘straddle’ the dura so that some solution reaches the CSF, and some the epidural space (Fig. 2). This may be exaggerated by the dura acting as a ‘flap’ valve across the needle opening. Initially, CSF pressure pushes the dura outwards so that aspiration is successful (Fig. 3A), but subsequent injection pushes the dura forward and the solution is misplaced (Fig. 3B).

A variant is that the needle tip penetrates the dura, but it is the arachnoid mater that acts as the flap valve so that a subdural injection results (Fig. 3C). This misplacement is usually thought of as leading to excessive spread during epidural block, but the equivalent phenomenon has been described after intended subarachnoid injection, and is a recognized complication of myelography. Subdural injection has also been identified as the cause of a failed block when either epidural or subarachnoid injection was intended.

These eventualities, being subtle abnormalities of placement, are impossible to identify at the actual time, but rotation of the needle through 360° after the initial appearance of CSF, and before check aspiration, has been advocated as a way of minimizing the possibility of them occurring, the theory being that the rotation reduces the risk of the membrane edges catching on the opening.

**Inadequate intrathecal spread**

The intrathecal spread of a local anaesthetic solution, even when correctly placed, has truly been described as capricious. The factors that affect it are many, but the focus here will be on those that may result in inadequate spread.

**Anatomical abnormality**

Intrathecal spread is governed by interplay between solution physical characteristics, gravity, and the configuration of the vertebral canal. Anatomical abnormalities that lead to problems with spread can be both overt and covert. The curves of the vertebral column are integral to solution

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**Fig 2** Possible positions of the tip of a pencil-point needle. If it is correctly placed (upper picture) all of the local anaesthetic solution will reach the subarachnoid space, but if the opening ‘straddles’ the dura (lower picture) some solution will be deposited in the epidural space.

**Fig 3** To show how the dura or arachnoid mater may act as a ‘flap’ valve across the opening of a pencil point needle. During aspiration (A) the dura/arachnoid are pulled back allowing CSF to enter the needle. During injection the dura (B) or arachnoid (C) is pushed forward and the local anaesthetic enters the epidural or subdural space.
spread and any obvious abnormality, kyphosis, or scoliosis, may interfere with the process. Examination of the patient should reveal whether this might occur, but it is not possible to predict whether the effect will be excessive spread or failure.

A very rare possibility, which is not apparent on examination, is that the ligaments that support the spinal cord within the theca form complete septae and act as longitudinal or transverse barriers to local anaesthetic spread. This can result in a block that is entirely unilateral or of insufficient cephalad spread. Spinal stenosis or other pathological lesions might also limit spread, effectiveness, or both, one such case being attributed to the consequences of previous intrathecal chemotherapy. Similarly, previous surgery within the vertebral canal may result in adhesions that interfere with spread.

An interesting ‘abnormality’ considered to have caused restricted spread in a single patient was a larger than usual volume of CSF in the lumbar theca. Subsequent systematic study has shown that lumbar CSF volume is the most important factor influencing the variability seen between individuals in the spread of an intrathecal injection. A negative correlation was found between lumbar CSF volume and the peak sensory level achieved with hyperbaric bupivacaine when the injection was performed in both supine and sitting positions. A variation of this factor is dural ectasia, which is a pathological enlargement of the dura seen in the majority of patients with Marfan’s syndrome and in some other connective tissue disorders.

**Solution density**

Consistently effective spinal anaesthesia requires that the practitioner has a good understanding of the factors that affect intrathecal spread, particularly, but not only, solution density. A solution with a density within the normal range of that of CSF (‘isobaric’) will virtually guarantee block of the lower limbs with little risk of thoracic nerve block and thus hypotension. However, plain solutions of bupivacaine, although often referred to as isobaric, are actually of sufficiently lower density to be hypobaric, especially at body temperature. As a result their range of spread is much less predictable than that of a truly isobaric preparation, and occasionally the block may be no higher than the first, or even second, lumbar dermatome when administered to the non-pregnant supine patient. Although the impact of variations in CSF volume has yet to be studied with these solutions, it seems likely that this factor may well be a factor in their variability.

Solutions with a density greater than that of CSF (hyperbaric) move very definitively under the combined influence of gravity and the curves of the vertebral canal. Over a hundred years ago, Barker, one of the early pioneers of spinal anaesthesia in the UK, observed that the addition of glucose to the solution made for a more reliable effect. In the standard scenario, that of a patient placed supine after the injection of a hyperbaric preparation at the mid-lumbar level, the solution will spread ‘down’ the slope under the effect of gravity to pool at the ‘lowest’ point of the thoracic curve, so exposing all nerve roots up to that level to an effective concentration of local anaesthetic. However, if lumbar puncture is performed at the fourth lumbar or the lumbo-sacral interspace the local anaesthetic may be ‘trapped’ below the lumbar curve, especially if the patient is in the sitting position during injection and maintained in that position for a period thereafter.

This results in a block that is restricted to the sacral segments, just as has been described with a spinal catheter that passes caudally. Prevention relies on avoiding too low an injection level unless, of course, a deliberate ‘saddle’ block is intended.

**Ineffective drug action**

The last possible explanation for a failed spinal is that the solution actually injected reaches the target nerves, but is inactive or ineffective, with a variety of explanations being possible.

**Identification errors**

Spinal anaesthetics are supplied in aqueous solution ready for injection and there is no opportunity for confusion in the preparation of the solution itself. However, other optically clear solutions, such as a separate local anaesthetic for skin infiltration or analgesic adjuvants, are often used from the same sterile preparation area and the possibility that confusing them may lead to an ineffective block must be considered. Recognition of the possibility of such injection errors has led to the widespread use of syringe labelling in anaesthesia, but this is not as easy within a sterile field as it is on an anaesthetic work station. Attention to detail is essential, but minimizing the number of ampoules on the block tray (such as using the same local anaesthetic for both skin infiltration and spinal) and consistent use of different sizes of syringe for each component of the procedure help considerably.

**Chemical incompatibility**

The mixing of two different pharmaceutical preparations also raises the possibility of ineffectiveness as a result of interaction between local anaesthetic and adjuvant. Local anaesthetics seem to be compatible with most of the common opioids, but there has been little formal study of the effects of mixing them, and the situation is even less definitive with other adjuvants such as clonidine, midazolam, and other more extreme substances. Certainly, there are no studies of the stability of three or more substances when mixed together for intrathecal use, a not unknown practice today. Chemical reaction might generate an obvious precipitate, but another possibility is that the pH of the local anaesthetic solution becomes even lower than it was to start with. This would decrease the concentration
of the un-ionized fraction that is what diffuses into nerve tissue and, unless the solution mixes well with CSF, a decreased effect could result. There is at least one report indicating that the incidence of failure is greater after the addition of a vasoconstrictor solution and this could represent an example of this effect.\(^{30}\)

**Inactive local anaesthetic solution**

The older, ester-type local anaesthetics are chemically labile so that heat sterilization and prolonged storage, particularly in aqueous solution, can make them ineffective because of hydrolysis and hence they need very careful handling. Although the more modern amide-linked drugs (e.g. lidocaine, bupivacaine, etc.) are much more stable and can be heat sterilized in solution and then stored for several years without loss of potency, there have been a number of reports attributing failure of spinal anaesthetics to inactive drug.\(^{81, 63, 84}\)

**Local anaesthetic resistance**

Very rarely a failed spinal anaesthetic has been attributed to physiological ‘resistance’ to the actions of local anaesthetic drugs, although the reports tend to the anecdotal.\(^{23, 36, 45}\) A history of repeated failure of dental or other local anaesthetic techniques is accompanied by speculation that the problem is because of a sodium-channel mutation that renders the drugs ineffective. However, no such mutation has ever been described, and the clinical reports are incomplete, specifically failing to consider not only the recognized causes of failure, but also the behaviour of an anxious patient preferring general anaesthesia as an explanation for the ‘resistance’. Very detailed investigation would be required for ‘resistance’ to be accepted as an explanation. As an aside, any patient giving a history of repeated failures with local anaesthesia should be managed by an experienced clinician.

**Failure of subsequent management**

Not all of a patient’s claims of discomfort, or even pain, during a spinal anaesthetic are the result of an inadequate injection. A properly performed spinal anaesthetic will produce complete somatic, and a major degree of autonomic, nerve block in the lower half of the body unless a specifically restricted method is used. However, ensuring that this block occurs is only part of the process because the unaffected components of the nervous system require consideration and management. Specifically, this relates to conscious awareness of the clinical setting and of ‘sensations’ transmitted through unblocked nerves, with both factors possibly making the patient claim that the block has failed. This may not actually be the case, but patient management certainly has failed if such a claim is made when the block is actually as good as it could be.

Lying supine and wide awake while undergoing surgery is not a pleasant experience, even for the most sanguine of individuals, and anxiety alone can cause much difficulty. Further, operating tables are designed for surgical access, not patient comfort; and intra-abdominal stimuli may result in afferent impulses in unblocked parasympathetic and phrenic nerve fibres. The more anxious the patient, the greater will be the impact of these factors and the more likely will it be that the patient will fail to cope with the situation and claim that the anaesthetic has not worked properly. Expectation plays a part, and good preoperative patient counselling followed by a supportive approach from the anaesthetist during the operation is important in avoiding such problems, but so is the judicious, and pro-active use of systemic sedative and analgesic drugs. Sufficient sedation to produce drowsiness, or even sleep (with appropriate monitoring), is rarely contra-indicated other than in the obstetric situation, and even there small doses may occasionally be useful.

**Testing the block**

In recent years, it has become almost mandatory, certainly in the obstetric setting, to test the level of block formally before surgery commences. This apparently sensible precaution may be difficult or impossible to undertake in some patients (for example the demented patient with a fractured neck of femur). Excessive focus on testing can also have a negative impact. Most patients will have some anxiety about the effectiveness of the injection, and this will be increased if testing is started too soon. Conventional practice is to check motor block by testing the ability to lift the legs, followed by testing of sensory block to stimuli such as soft touch, cold, or pin prick, all of which have their proponents. It is advisable to start testing in the lower segments, where onset will be fastest, and work upwards. Proving early on that there is some effect encourages patient confidence; testing too soon does the opposite.

Even if there is no formal assessment of the level of block, the clinician must be confident that an adequate block has been produced. Establishing that the level of block is appropriate for the projected surgery is often taken to demonstrate that the quality of block is adequate also, but this is not always the case if cold or pin-prick stimuli are used. The observation that the upper block level is a few dermatomes above which innervate the surgical field (not forgetting the deeper structures) is a good start, but it does not guarantee that the quality of block is sufficient. A covert pinch of the site of the proposed surgical incision may be a better indicator of skin analgesia, and can be reassuring if the block has been slow in onset. Indeed, there is much to be said, particularly when the patient is conscious, for asking the surgeon to do the same with a toothed surgical forceps before incising the skin,\(^{10}\) but surreptitiously and without asking a loaded question such as ‘Does that hurt?’! The patient is distracted by conversation and an exchange of glances between surgeon and anaesthetist is all that is needed for surgery to begin.
Catheter and combined techniques
The great majority of spinal anaesthetics involves a single, through needle injection and, as has been noted, this requires some certainty about its effectiveness for surgery. To take advantage of the rapid onset and profound block of spinal anaesthesia, both continuous and combined spinal–epidural techniques have been introduced to increase flexibility. If the catheters are correctly placed, problems of inadequate spread, quality, and duration of effect can be dealt with although many of the potential technical problems outlined above can still apply. However, both methods require a greater level of skill and experience to use, the insertion of an intrathecal catheter can be surprisingly difficult to achieve in some patients and, as has been mentioned already, can result in the misdirection of the local anaesthetic solution, with the risk of neurotoxicity. It is vital to leave no more than 2–3 cm of catheter within the dura to avoid this. In the combined technique, it is common to inject a relatively small volume for the spinal component, so the problems that can result in a proportion not reaching the subarachnoid space are very relevant, but at least the epidural catheter can be used in attempts to rescue the situation.

Management of failure
Failure of a spinal anaesthetic is an event of significant concern for both patient and anaesthetist even when it is immediately apparent, but it can have serious consequences (clinical and medico-legal) if the problem only becomes evident once surgery has started. If there is any doubt about the nature or duration of the proposed surgery, a method other than a standard spinal anaesthetic should be used. The trainee anaesthetist should avoid over-selling the technique, especially in the early days of unsupervised practice. Promising that all will be achieved by one injection leaves no room for manoeuvre, but offering one injection to reduce pain and a second to ensure unconsciousness does. If a spinal anaesthetic does fail in some way, the management options are limited; so, the first rule is to expend every effort in prevention.

Prevention is better than cure
Having made the decision to use a spinal anaesthetic, the block should be performed with meticulous attention to detail as has been indicated above. It is impossible to over-emphasize this point.

The failed block
The precise management of the failed block will depend on the nature of the inadequacy and the time at which it becomes apparent. Thus, some monitoring of the onset of the block and correct interpretation of the observations are both vital. The slower the onset of either motor or sensory block, the more likely is the block to be inadequate, so the more detailed this assessment should be. While the onset of spinal anaesthesia is rapid in most patients, it can be slow in some; so, ‘tincture of time’ should always be allowed. However, if most of the expected block has not developed within 15 min, some additional manoeuvre is almost certainly going to be needed. The possibilities, their explanations, and suggested immediate responses are as follows:

(1) No block: the wrong solution has been injected, it has been deposited in the wrong place, or it is ineffective. Repeating the procedure or conversion to general anaesthesia are the only option. If, after operation, the patient has significant pruritus, it is likely that only an opioid was injected.

(2) Good block of inadequate cephalad spread: the level of injection was too low, anatomical abnormality has restricted spread, or some injectate has been misplaced. If a hyperbaric solution was used, flex the patient’s hips and knees and tilt the table head down. This straightens out the lumbar curve, but maintains a cephalad ‘slope’ and allows any solution ‘trapped’ in the sacrum to spread further. A variation with the same aim, but perhaps better suited to the obstetric situation, is to turn the patient to the full lateral position with a head down tilt, reversing the side after 2–3 min. If a plain (and usually slightly hypobaric) solution has been used, it may help to sit the patient up, but beware of peripheral pooling of blood.

If a spinal catheter injection results in inadequate spread, the response should not be to inject more of the same solution because dose has minimal effect on intrathecal spread. Either posture should be manipulated as above, or a different baricity of solution should be tried, or the catheter should be withdrawn before the injection is repeated.

(3) Good, but unilateral block: this is most likely because of positioning, but it is possible that longitudinal ligaments supporting the cord have blocked spread. If the operation is to be on the anaesthetized limb, then the surgeon should know that the other leg has sensation, and the patient should be reassured and closely monitored. Otherwise, turning the patient onto the unblocked side if a hyperbaric solution was used (or the reverse for plain solutions) may facilitate spread.

(4) Patchy block (This term is used to describe a block that appears adequate in extent, but the sensory and motor effects are incomplete.): causes of inadequate block are numerous and include all those discussed above, but the most likely explanation is that the local anaesthetic was at least partially misplaced, or that the dose given was inadequate. If this becomes apparent before surgery starts, the options are to repeat the spinal injection or to use a greater degree of systemic supplementation than was planned, the latter being the
only option after skin incision. It may not be necessary to recourse to general anaesthesia, sedation, or analgesic drugs often being sufficient especially when patient anxiety is a major factor. Infiltration of the wound and other tissues with local anaesthetic by the surgeon may also be useful in such situations.

(5) **Inadequate duration:** the most likely explanation is that for one of several reasons an inadequate dose of local anaesthetic was delivered to the CSF. Alternatively, lidocaine (intended for skin infiltration) was confused for bupivacaine, or the operation has taken longer than expected. Systemic supplementation or infiltration of local anaesthetic may tide matters over, but often the only option is to convert to general anaesthesia.

**Repeating the block**

Where no effect at all has followed the injection it seems reasonable to repeat the procedure, paying close attention to avoiding the potential pitfalls. In all other situations besides total failure, there must be some local anaesthetic in the CSF already, and anxieties relating to several issues have to be taken into account:

(1) A restricted block may be because of some factor, probably anatomical, impeding the physical spread of the solution, and it may have exactly the same impact on a second injection, resulting in a high concentration of local anaesthetic at or close to the site of injection. Cauda equina lesions were described after continuous spinal anaesthesia when very restricted spread prompted repeat injections rather than the manipulation of other factors, and a similar problem has been described after repeated needle injection.

(2) Repeat injection, especially in response to a poor quality block, may lead to excessive spread, so it may be argued that a lower dose should be used to reduce the risk of this possibility.

(3) A good quality, but unilateral block, might lead to an attempt to place a second injection into the ‘other’ side of the theca, but the risk of placing the second dose in the same side must be significant.

(4) Barriers to spread within the subarachnoid space may also affect epidural spread (and vice versa), so an attempt at epidural block may not succeed either.

(5) A block of inadequate cephalad spread might be overcome by repeating the injection at a higher level, but should perhaps only be attempted when the indication for a regional technique is considerable.

(6) The final concern, particularly applicable to the last mentioned, but relevant to nearly all situations where a repeat block might be considered, is that the adjacent nerve tissue is already affected by local anaesthetic action so that the risk of direct needle trauma is increased.

Only some of these problems have actually been described, most being in the category of theoretical possibilities, but such concerns do reinforce the view that every effort must be made to ensure that the first injection is fully effective.

**Recourse to general anaesthesia**

There are many ways in which an inadequate block might be ‘rescued’, but there is a limit to how much discomfort or distress an individual patient can tolerate, so general anaesthesia must be considered if one or two simple measures have not rectified matters. Common sense and clinical experience are usually the best indicators of exactly when to convert to general anaesthesia, so the unsupervised trainee can be at a disadvantage. However, it is far better to make the decision sooner rather than later and have to deal with a seriously distressed patient. Of course, explaining later why the anticipated technique had not been provided can be difficult. It is another reason why prevention (getting the block right to start with) is the best approach, but it is also a reason for not ‘over-selling’ the regional approach before operation.

If general anaesthesia is induced to supplement a partially effective spinal anaesthetic, any degree of sympathetic nerve block will make hypotension more likely.

**Follow-up initiatives**

**Clinical follow-up**

As with any anaesthetic complication, the details should be documented fully in the notes, and the patient provided with an apology and a full explanation after operation. Giving the patient a written summary of events for presentation to a future anaesthetist can be very helpful, although care should be taken to prevent medico-legal recourse. Rarely, inadequate spread has been the first indication of pathology within the vertebral canal. Therefore, it may be appropriate to look for symptoms and signs of neurological disease, and involve a neurologist if there is any suspicion of these being present.

It is during the follow-up of a patient in whom no block was obtained, the possibility of local anaesthetic ‘resistance’ may seem an attractive explanation. As has already been noted, much wider consideration of the possibilities, supported by very detailed investigation, is needed than has been the case in previous reports.

**Investigating local anaesthetic effectiveness**

Spinal anaesthesia is usually a simple and effective technique, but ‘failure’ can occur at any time and in the hands of any clinician, no matter how experienced. However, if the procedure has, apparently, been routine and straightforward concerns can arise that the current supply of local anaesthetic is defective, especially if two or more such failures occur in the same hospital within a short period of time. The preparations which have been most implicated
are those of hyperbaric bupivacaine (probably because it is the drug used most commonly at present), with drug from both major suppliers, Abbott8 16 44 being involved. In fact, the chemical stability of the amide drugs and modern standards of pharmaceutical manufacture mean that drug inactivity is a most unlikely cause of a failed spinal anaesthetic, but it remains a possibility which at least has to be eliminated.

As has been suggested, performing skin infiltration with some of the solution intended for the spinal injection should demonstrate that it is effective. If the concern continues the operating theatre, pharmacy and anaesthetic department records should be cross-checked to see whether other practitioners in the hospital have experienced any problems. Similarly, distributors should be able to check whether other hospitals which have been supplied with material from the same batch have reported difficulty. If such enquiries reveal that others are using the same material, the clinician should consider the advice of those two great authorities, Lee and Atkinson, on ‘The spinal that does not take’.

All experienced workers have encountered this occasionally even though accepted procedure has apparently been followed. Reflection, however, usually discloses some flaw in technique. In 1907 Alfred E. Barker wrote that for successful spinal analgesia it is necessary ‘to enter the lumbar dural sac effectually with the point of the needle, and to discharge through this, all the contemplated dose of the drug, directly and freely into the cerebrospinal fluid, below the termination of the cord’ (Barker, 1907). Failure to follow the details of this advice is the commonest cause of a poor result.27

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Disclosure of Risks Associated With Regional Anesthesia: A Survey of Academic Regional Anesthesiologists


Background and Objectives: In view of the relatively few large studies available to estimate the rates of complications following regional anesthesia, we aimed to identify and quantify the risks that academic regional anesthesiologists and regional anesthesia fellows disclose to their patients before performing central and peripheral nerve blockade.

Methods: We asked 23 North American regional anesthesia fellowship program directors to distribute a questionnaire to the regional anesthesiologists and regional anesthesia fellows at their institutions. The questionnaire was designed to capture the risks and corresponding incidences that are routinely disclosed to patients before performing the most common central and peripheral nerve block techniques.

Results: The total number of respondents was 79 from 12 different institutions. Fifty-eight (74%) respondents disclose risks of regional anesthesia in order to allow their patients to make an informed choice, whereas 20 (26%) disclose risks for medicolegal reasons. For central neural blockade, the most commonly disclosed risks are headache, local pain/discomfort, and infection. For peripheral nerve blockade, the most commonly disclosed risks are transient neuropathy, local pain/discomfort, and infection. For both central and peripheral nerve blockade, the risks most commonly disclosed are also those with the highest-reported incidences.

Conclusions: The risks of regional anesthesia most commonly disclosed to patients by academic regional anesthesiologists and regional anesthesia fellows are benign in nature and occur frequently. Severe complications of regional anesthesia are far less commonly disclosed. The incidences of severe complications disclosed by academic regional anesthesiologists and their fellows can be inconsistent with those cited in the contemporary literature. Reg Anesth Pain Med 2007;32:7-11.

Key Words: Adverse effects, Anesthesia, Epidural, Spinal, Nerve block, Postoperative complications.

Complications after regional anesthesia (RA) are uncommon. Unfortunately, prohibitively large numbers of patients are required for study in order to capture the true incidences of such complications. The American Society of Anesthesiologists (ASA) Closed Claims Project provides the largest collection of adverse events associated with modern RA practice in the United States; however, the lack of a denominator prevents the calculation of incidence. The objective of this study is to identify and quantify the risks of RA that are routinely disclosed by academic regional anesthesiologists and their RA fellows to patients in North American teaching hospitals. The information gathered may complement the relatively limited data available in the contemporary literature to produce a more accurate representation of the risks associated with RA and allow other anesthesia practitioners to draw on the experience of experts during preoperative discussions with their patients. Our hypothesis was that academic regional anesthesiologists and RA fellows...
routinely disclose all significant risks and corresponding incidences to their patients before performing central (CNB) or peripheral nerve blockade (PNB).

Methods

After institutional review board approval (University Health Network, Toronto, Ontario, Canada), an information letter and questionnaire were sent by electronic mail to all identifiable regional anesthesia fellowship program directors in North America on November 7, 2005. Twenty-three program directors were identified from the Regional Anesthesia Fellowship Program listings on the American Society of Regional Anesthesia and Pain Medicine website (www.ASRA.com) as well as the recently published guidelines for RA Fellowship training.³ The program directors were asked to distribute the questionnaire to “all practicing regional anesthesiologists and RA fellows” at their home institutions and then return the completed questionnaires by mail or facsimile. After 8 weeks, a reminder message was sent by electronic mail to those program directors who had not yet responded to the initial request.

The questionnaire was primarily designed to capture the risks and corresponding incidences that are routinely disclosed by the respondents to their patients prior to performing the most common CNB and PNB techniques. From a list of complications for each CNB and PNB technique, the respondents were instructed to select which risks they routinely disclose to their patients and indicate the corresponding incidence that is disclosed along with each risk according to a 6-point scale: (1) “greater than 1:10,” (2) “approximately 1:100,” (3) “approximately 1:1,000,” (4) “approximately 1:10,000,” (5) “approximately 1:100,000,” or (6) “less than 1:1,000,000.” Respondents were encouraged to add any risks (and corresponding incidences) that did not appear in the list. Additionally, respondents were asked to select the “primary reason” for disclosing risks associated with RA from 2 options: (1) “to allow the patient to make an informed choice” or (2) “for medicolegal reasons.” Finally, respondents were asked to select whether their institution required a “written consent form” for (1) “general anesthesia,” (2) “regional anesthesia,” (3) “combined (general/regional anesthesia),” or (4) none of the above.

Data analysis was undertaken using SAS Version 8.0 (SAS Institute Inc., Cary, NC). Categorical data were analyzed by using the chi-square test. Non-parametric data were analyzed by using the Mann-Whitney U test with the Bonferroni correction for multiple comparisons.

Results

The program directors from 12 institutions (9 American and 3 Canadian) replied and agreed to participate in this study. Seven program directors replied and agreed after the initial e-mail request, whereas 5 replied and agreed after the reminder e-mail request. No replies were received from the program directors of the remaining 11 institutions. The total number of respondents (questionnaires returned) was 79 (70 attending anesthesiologists and 9 RA fellows). Fifty-eight (74%) respondents answered that the primary reason for explaining regional anesthetic risks was to allow their patients to make an informed choice regarding anesthetic technique, whereas 20 (26%) answered for medicolegal reasons. Among the 12 participating institutions, 8 require a written consent form for anesthesia, whereas the remaining 4 institutions do not. For all 8 institutions that require a written consent form for anesthesia, both general anesthesia (GA) and RA are addressed in a single form. The risks and corresponding incidences routinely disclosed for spinal and epidural anesthesia are remarkably similar. For both spinal and epidural anesthesia, the most commonly disclosed risks are headache, local pain/discomfort, and infection (Table 1). Severe complications of CNB, such as paralysis, cardiac arrest, and death, are far less frequently disclosed. For PNB, the most commonly disclosed risks are transient neuropathy, local pain/discomfort, and infection (Table 2). The 2 exceptions are axillary block, where bruising is often disclosed (possibly reflecting the transarterial technique), and ankle block, where the risk of neuropathy is arguably rare. For both CNB and PNB, the risks most commonly disclosed are also those with the highest likelihood of occurrence among all incidences routinely disclosed by our respondents (Tables 1 and 2). When analyzed according to institutional country of origin (United States v Canada), there were no significant differences for any of the responses in the questionnaire.

Discussion

Neurological complications of RA can be severe and potentially devastating to patients and their families. Candid disclosure and accurate quantification of risks associated with RA are imperative to protecting both patients and anesthesiologists alike. Surprisingly, however, the results of our questionnaire suggest that relatively few regional anesthesiologists disclose the severe risks of RA. For exam-
ple, only 58% and 43% of academic regional anesthesiologists routinely disclose the risks of permanent neuropathy and paralysis, respectively, to their patients undergoing CNB. Our survey did not enable us to determine why some anesthesiologists failed to disclose these risks. One possible explanation for this finding is the potential for discussions regarding anesthetic risk in the immediate preoperative period to exacerbate the patients’ preoperative anxiety. 

Additionally, previous studies that have examined which anesthetic risks patients would like to know about are conflicting. Many patients prefer simple explanations about the main risks and benefits, although a considerable number of patients wish full-risk disclosure. Nonetheless, anesthesiologists have a duty to accurately disclose the significant risks of the proposed anesthetic to their patients, including those that happen relatively frequently (e.g., local pain/discomfort) as well as those that happen rarely but are severe in nature (e.g., permanent neuropathy and paralysis).

The complications of RA and their likelihood presented to the patient by the anesthesiologist likely influence the patients’ choice of anesthetic technique for their surgery. Disclosing an inflated rate of complications may cause patients to opt for GA and forfeit the potential benefits of RA. Alternatively, failing to mention certain complications or deflating the rate of complications associated with RA may lead the patient to choose an RA technique when the patient would have chosen a GA had the risks been accurately disclosed. Importantly, among the anesthesiologists who do disclose the severe risks of CNB, specifically, permanent neuropathy, paralysis, respiratory failure, seizures, cardiac arrest, and death, the incidences disclosed are generally in keeping with those cited in the contemporary literature. The single exception is seizures after CNB, which reportedly occur far less often (0.12-1.32:10,000) than what is disclosed by our respondents. For PNB, the contemporary literature suggests that the incidence of severe complications is considerably less common than that disclosed by our respondents. For example, in 2 recent comprehensive prospective studies of complications after PNB, yielding 5,412 blocks in aggregate, there were no cases of permanent neuropathy, 1 case of seizure (1.8:10,000), and no cases of cardiac arrest or death. Similarly, in the large and widely cited investigation of 43,552 PNBs (excluding lumbar plexus block) by Auroy and colleagues, there were 5 cases of seizure (1.1:10,000) and no cases of cardiac arrest or death. Unfortunately, Auroy’s study did not provide sufficient detail to determine the rate of permanent neuropathy after PNB. There are at least 2 possible explanations for the discrepancy.

### Table 1. Risks of Neuraxial Block Disclosed by Regional Anesthesiologists

<table>
<thead>
<tr>
<th>Local Pain/Discomfort</th>
<th>Bruising</th>
<th>Infection</th>
<th>Headache</th>
<th>Transient Neurological Symptoms</th>
<th>Peripheral Neurpathy (transient)</th>
<th>Peripheral Neurpathy (permanent)</th>
<th>Paralysis</th>
<th>Seizures</th>
<th>Respiratory Failure</th>
<th>Cardiac Arrest</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>69</td>
<td>55</td>
<td>69</td>
<td>45</td>
<td>37</td>
<td>44</td>
<td>43</td>
<td>10</td>
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<td>13</td>
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<tr>
<td>%</td>
<td>37</td>
<td>90</td>
<td>37</td>
<td>90</td>
<td>49</td>
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<td>49</td>
<td>49</td>
<td>5</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10</td>
</tr>
</tbody>
</table>

N, number of respondents who routinely disclose specified risk; %, percentage of total respondents who routinely disclose specified risk; incidence, incidence of specified risk routinely disclosed by respondents. The incidence is expressed as the mode calculated from all responses in aggregate; N/A, not applicable.

Risk Disclosure for Regional Anesthesia • Brull et al. 9
Table 2. Risks of Peripheral Nerve Blockade Disclosed by Regional Anesthesiologists

<table>
<thead>
<tr>
<th></th>
<th>Local Pain/Discomfort</th>
<th>Bruising</th>
<th>Infection</th>
<th>Horner's Syndrome</th>
<th>Peripheral Neuropathy (transient)</th>
<th>Peripheral Neuropathy (permanent)</th>
<th>Paralysis</th>
<th>Seizures</th>
<th>Pneumothorax</th>
<th>Respiratory Failure</th>
<th>Cardiac Arrest</th>
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<td></td>
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<td></td>
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<tr>
<td>N</td>
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<td>54</td>
<td>55</td>
<td>57</td>
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<td>15</td>
<td>29</td>
<td>27</td>
<td>23</td>
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</tr>
<tr>
<td>%</td>
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<td>55</td>
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<td>71</td>
<td>73</td>
<td>77</td>
<td>21</td>
<td>39</td>
<td>37</td>
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<td>18</td>
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<td>1:10^2</td>
<td>1:10^4</td>
<td>1:10</td>
<td>1:10^2</td>
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<tr>
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<td>45</td>
<td>39</td>
<td>45</td>
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<td>47</td>
<td>43</td>
<td>N/A</td>
<td>17</td>
<td>29</td>
<td>N/A</td>
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<td>18</td>
</tr>
<tr>
<td>%</td>
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<td>60</td>
<td>70</td>
<td></td>
<td>72</td>
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<td>N/A</td>
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<td>46</td>
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<td>30</td>
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<tr>
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<td>1:10^2</td>
<td>1:10^4</td>
<td>1:10</td>
<td>1:10^4</td>
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<tr>
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<td>55</td>
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<td>N/A</td>
<td>54</td>
<td>51</td>
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<td>21</td>
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<tr>
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<td>70</td>
<td></td>
<td>73</td>
<td>70</td>
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<td>Femoral block</td>
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<tr>
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<td>51</td>
<td>46</td>
<td>54</td>
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<td>48</td>
<td>N/A</td>
<td>18</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>%</td>
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<td>62</td>
<td>73</td>
<td></td>
<td>71</td>
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<td>N/A</td>
<td>18</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>%</td>
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<td>61</td>
<td>74</td>
<td></td>
<td>73</td>
<td>69</td>
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<td>26</td>
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<tr>
<td>Incidence</td>
<td>1:10</td>
<td>1:10</td>
<td>1:10^5</td>
<td>1:10</td>
<td>1:10^4</td>
<td>1:10^4</td>
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<td>%</td>
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<td>45</td>
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<td>1:10</td>
<td>1:10^4</td>
<td>1:10</td>
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<td>1:10^5</td>
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</tr>
</tbody>
</table>

N, number of respondents who routinely disclose specified risk; %, percentage of total respondents who routinely disclose specified risk; incidence, Incidence of specified risk routinely disclosed by respondents. The incidence is expressed as the mode calculated from all responses in aggregate; N/A, not applicable.
between the incidence of severe complications disclosed by our respondents and that reported in the literature. The first may be that regional anesthesiologists are less familiar with the contemporary literature than they should be. The second, perhaps more palatable explanation, is that much of the available literature is flawed, and the respondents are drawing on their own clinical experience to estimate and disclose the incidences of severe complications associated with RA. Indeed, the questionable validity of the available literature limits its role in guiding discussions of risk with patients. The largest contemporary studies of risk associated with RA are restricted to reviews of insurance claims and self-reporting by anesthesiologists, both of which can result in misrepresentation of risk.

There are several important limitations of our study. First, because the distribution of our survey was left to the discretion of the program directors, we did not determine the total number of questionnaires distributed and therefore could not calculate a true “response rate.” Moreover, the rate of reply by the program directors was only 12 out of the 23 programs identified; however, it is likely that some of the e-mail contact information gathered was outdated and/or the programs inactive or discontinued. Furthermore, although we recognize that the inclusion of RA fellows may have skewed our results, any such bias is likely minimal. Indeed, the number of RA fellow respondents was very low compared to the number of attending anesthesiologist respondents. We, nonetheless, believe that including RA fellows is important because fellows are often the ones charged with conducting the preoperative assessment and entering into discussions of risk with their patients; such discussions should faithfully reflect the practice of their expert instructors, namely the attending anesthesiologists. Finally, the incidence of some complications disclosed by our respondents may not be generalizable beyond teaching centers. For example, the incidence of headache routinely disclosed for either spinal or epidural anesthesia was curiously similar and questionably high.

In summary, our survey of risk-disclosure practices among academic regional anesthesiologists and RA fellows revealed that the most commonly disclosed risks of RA are benign in nature and occur frequently. Severe complications of RA are far less commonly disclosed. The incidences of severe complications disclosed by academic regional anesthesiologists and their fellows can be inconsistent with those cited in the contemporary literature.

References

In this issue of *Regional Anesthesia and Pain Medicine*, Brull et al. described what risks were disclosed to patients by academic anesthesiologists and anesthesia fellows in North American regional-anesthesia fellowship programs in obtaining informed consent for regional anesthesia. Brull et al. found the most commonly revealed risks were benign in nature and occurred frequently. For central neural block, the most commonly disclosed risks were headache, local pain/discomfort, and infection, whereas for peripheral-nerve block, transient neuropathy, local pain/discomfort, and infection were mentioned. Severe complications of regional anesthesia, including permanent neurologic injury, paralysis, cardiac arrest, seizures, and death were only infrequently disclosed in the process of informed consent. For instance, a minority of anesthesiologists described risks of paralysis (43%), seizures (20%), cardiac arrest (14%), and death (29%) to patients undergoing epidural anesthesia. In addition, the authors found that the incidences of severe complications cited by the anesthesiologists were often inconsistent with the literature.

Although the results of Brull et al. are probably typical of the practice of regional anesthesia, the results are concerning because of the ethical and legal requirement for informed consent. Informed consent requires an active communication between the physician and patient, in which the physician explains the nature and purpose of the proposed procedure and the alternative techniques available, as well as a description of the risks and benefits of the procedures and alternatives. The desired outcome is that the patient will have sufficient knowledge to make an educated choice about whether to undergo the proposed procedure or treatment.

What types of risks need to be disclosed during the process of informed consent? Although the exact information to be transmitted varies from state to state, most states have adopted a “reasonable patient” standard. This standard requires the physician to disclose information that a reasonable patient under similar circumstances would want to know to make an informed decision. Informed consent requires that a patient have a full understanding of that to which he or she has consented. The risks that should be disclosed are those that would be important in deciding whether to undertake the proposed therapy. For regional anesthesia, the disclosure should include both the common, but not severe, risks (e.g., local pain/discomfort, infection, headache, transient neuropathy) and the rare, but of major consequences, risks (e.g., seizure, cardiac arrest, permanent neuropathy, paralysis, and death). Certainly, a patient would want to know a risk of permanent neuropathy exists after an interscalene block performed for post-operative pain control, especially if he or she were an artist, pianist, or a surgeon.

Interestingly, 3 out of 4 of the programs utilized a written informed consent for anesthesia, with most addressing general and regional anesthesia on a single form. Although the Joint Commission on Accreditation of Healthcare Organizations requires documentation of informed consent, it can be done by handwritten note, on the surgical consent, or on a separate written anesthesia consent form. Many attorneys believe that a written anesthesia-specific consent form, detailing se-
lected risks specific to the procedure will help in the defense of a claim for an injury.\textsuperscript{4,5} Notations to tailor the informed-consent discussion to a specific patient help to support the defense of the underlying medical issues.\textsuperscript{5} Although informed consent is seldom the major issue of liability in a claim,\textsuperscript{5,6} in a significant number of cases, the adequacy of informed consent is included as an additional allegation, thereby influencing the evaluation, defense, and resolution of a malpractice claim.\textsuperscript{5} However, patients can still allege lack of understanding of risks in the presence of a written consent form.\textsuperscript{4} Likewise, no scientific evidence indicates that separate anesthesia written informed consent is better than a handwritten note plus the written surgical consent.\textsuperscript{7}

In summary, the article by Brull et al.\textsuperscript{1} brings to our consciousness the need to further educate our patients of important risks/benefits of all types of anesthesia, especially regional anesthesia. To make an informed decision, patients require accurate portrayal of rare, serious complications, as well as the more common minor ones.

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University of Washington School of Medicine
Seattle, WA

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The Role of Intrathecal Drugs in the Treatment of Acute Pain

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Department of Anesthesiology, University of Vermont College of Medicine, Burlington, Vermont

Intrathecal opioids are widely used as useful adjuncts in the treatment of acute and chronic pain, and a number of non-opioid drugs show promise as analgesic drugs with spinal selectivity. In this review we examine the historical development and current use of intrathecal opioids and other drugs that show promise for treating pain in the perioperative period. The pharmacology and clinical use of intrathecal morphine and other opioids is reviewed in detail, including dosing guidelines for specific surgical procedures and the incidence and treatment of side effects associated with these drugs. Available data on the use of non-opioid drugs that have been tested intrathecally for use as analgesics are also reviewed. Evidence-based guidelines for dosing of intrathecal drugs for specific surgical procedures and for the treatment of the most common side effects associated with these drugs are presented.

(Anesth Analg 2005;101:S30–S43)

Opioid analgesics have long been recognized as among the most effective treatments for pain. In his treatise on gout and rheumatism (1), the 17th century English physician Thomas Sydenham wrote: “Among the remedies which it has pleased Almighty God to give man to relieve his suffering, none is so universal and so efficacious as opium.”

Despite their nearly universal ability to alleviate pain, opioids have a number of unpleasant, even life-threatening, side effects: nausea and vomiting, tolerance, pruritus, urinary retention, and respiratory depression. For thousands of years, these medications were used without a known mechanism of action until 1971, when a class of highly specific opioid receptors was identified (2). Soon thereafter, opioid receptors were localized within the brain (3) and spinal cord (4). Evidence that direct application of morphine at the spinal cord level could produce spinally mediated analgesia soon followed (5). Based on this limited experimental evidence, Wang et al. (6) administered bolus intrathecal morphine and Onofrio et al. (7) reported chronic intrathecal morphine infusions, both working in patients with severe pain associated with advanced cancer; they reported the first observations of profound and prolonged pain relief with spinal opioids. Since these first, bold clinical experiments, we have witnessed a rapid transition from the laboratory to clinical practice. Intrathecal opioids are now widely used as useful adjuncts in the treatment of acute and chronic pain, and a number of non-opioid drugs show promise as analgesics with spinal selectivity. In this review, we examine the current use of intrathecal opioids and other drugs that show promise for treating pain in the perioperative period.

Search Strategy

We performed a MEDLINE search for all indexed articles published between 1966 and March 2004 using the search terms “postoperative pain,” “spinal or intrathecal,” “spinal analgesia,” “intrathecal analgesia,” “acute pain and spinal,” and “postoperative pain and spinal,” resulting in 1436 articles. The abstracts of all articles were reviewed to select articles on the development and use of intrathecal drugs that are representative of the current state of our knowledge. Those articles representing the best available evidence were selected (e.g., randomized, controlled trials were used in preference to observational studies when available, case reports or case series were used only when no other information was available, and retrospective analyses were generally omitted); however, there was no attempt to assign qualitative scores to each article or to combine the available data quantitatively.

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S30 Anesth Analg 2005;101:S30–S43
**Pharmacology**

Drug disposition after intrathecal administration varies depending on the lipid solubility of the individual drug, and the most closely studied drugs are the opioid analgesics. After spinal administration, typically within the cerebrospinal fluid (CSF) in the lumbar cistern, the drug is distributed within CSF. Ummenhofer et al. (8) reported a series of elegant experiments in which the concentration of morphine, fentanyl, sufentanil, and alfentanil were measured within CSF, spinal cord, epidural fat, and plasma in anesthetized pigs after lumbar intrathecal administration. From their data, they developed a multiple-compartment pharmacokinetic model that closely simulates the observed pharmacology and explains many of the clinical characteristics of the opioids used for intrathecal analgesia. The fate of opioids after intrathecal administration is complex (Fig. 1). Intrathecal opioids penetrate the spinal cord and the dura mater to enter the epidural space. Within the spinal cord, they bind to nonspecific sites within the white matter as well as to specific receptors within the dorsal horn. Drug within the spinal cord eventually reaches the plasma compartment though venous uptake. In the epidural space, the opioid is sequestered in fat and enters the plasma compartment via venous uptake. The sum of these multiple avenues for drug disposition results in the clinical characteristics observed. Any drug given intrathecally rapidly redistributes within the CSF; opioid is detectable in the cisterna magna after lumbar intrathecal administration within 30 min, even with lipophilic drugs like sufentanil (9). Indeed, all opioids move within the CSF and this rapid distribution within the CSF likely accounts for the small, but significant, incidence of respiratory depression that is observed immediately after lumbar intrathecal injection (Fig. 2) (10).

The lipophilic opioids rapidly traverse the dura where they are sequestered in the epidural fat and enter the systemic circulation; they also rapidly penetrate the spinal cord where they bind to both nonspecific sites within the white matter as well as dorsal horn receptors and eventually enter the systemic circulation as they are cleared from the spinal cord. This rapid transfer from the CSF to both spinal cord and the epidural fat accounts for the rapid onset and the prompt decline in CSF levels of opioid, accounting for the minimal rostral spread, lack of delayed respiratory depression, and relatively small dermatomal band of analgesia seen during chronic administration; vascular uptake accounts for the limited duration of analgesia of lipophilic opioids (Fig. 3).

Morphine, the prototypic hydrophilic opioid, undergoes a similar transfer to both the spinal cord and the epidural space; however, there is limited binding to fat within the epidural space and limited binding to nonspecific receptors within the spinal cord white matter. Transfer to the systemic circulation is likewise slower than the lipophilic drugs. Concentrations within the CSF decline more slowly than similar doses of lipophilic drugs, accounting for the greater degree of rostral spread, delayed respiratory depression (Fig. 2), and extensive dermatomal analgesia during chronic administration. This complex pharmacokinetic behavior explains why the location of injection for intrathecal administration remains an important determinant in the pattern of analgesia observed (11). Hydrophilic drugs result in slow onset and a wide band of analgesia surrounding the site of injection. In contrast, highly lipophilic drugs transfer rapidly from the systemic circulation as they are cleared from the spinal cord. This complex pharmacokinetic behavior explains why the location of injection for intrathecal administration remains an important determinant in the pattern of analgesia observed (11). Hydrophilic drugs result in slow onset and a wide band of analgesia surrounding the site of injection. In contrast, highly lipophilic drugs transfer rapidly from...
the CSF and result in a broad band of analgesia that is much shorter in duration and the clinical observation that analgesia during prolonged infusion is limited to a narrower band of analgesia surrounding the anatomic site of administration during epidural administration (Fig. 4). The clinical dose range, onset, and duration of activity for various intrathecal opioids are shown in Table 1.

Internationally, opioids and adjuvant analgesics are supplied in varying concentrations and in preparations that include preservatives. Although the toxicity of the most common preservatives appears to be small (12), benzyl alcohol and the parabens have been implicated as the cause of neurotoxicity after intrathecal administration (13).

**Morphine**

In early trials with intrathecal morphine, doses ranged from 500–1000 μg and profound sedation and respiratory depression were not uncommon (14). In a carefully controlled study in healthy volunteers, profound and prolonged respiratory depression was observed in all subjects who received 600 μg of intrathecal morphine (15). In more recent years, several trials have examined doses as small as 40 μg, typically, extending only as large as 300 μg. Indeed, it appears that the efficacy of doses above this range is often limited by side effects.
In recent years, clinical investigation surrounding use of intrathecal morphine in the perioperative period has centered on establishing the optimal dose for specific surgical procedures. Rathmell et al. (16) compared the need for supplemental IV morphine via patient-controlled analgesia after doses of intrathecal morphine ranging from 0–300 μg after total hip and knee arthroplasty. After total hip replacement, intrathecal morphine (200 μg) provided excellent analgesia. In contrast, the degree of pain experienced after total knee arthroplasty exceeded the analgesia afforded by even the largest dose of intrathecal morphine (300 μg), yet patients who received this dose nearly universally reported nausea, vomiting, and pruritus. Intrathecal morphine has been studied as an analgesic for pain after cesarean delivery (17), various orthopedic procedures (16), and a range of other surgical procedures (18) from spinal (19) to cardiac surgery (20). Two generalizations emerge. The first and most important is that the optimal dose of intrathecal morphine depends on the specific surgical procedure, with doses <100 μg often sufficing for pain control after cesarean delivery, whereas doses in the area of 500 μg may be required for more extensive surgery, such as thoracotomy or open abdominal aortic aneurysm repair. The best available evidence relating to optimal dosing for specific procedures is presented in Table 2. The second generalization is that the incidence of side effects increases in proportion to the dose administered, with doses in excess of 300 μg producing nausea, vomiting, pruritus, and urinary retention in most recipients. Indeed, there appears to be a ceiling analgesic effect for intrathecal morphine above which the risk of side effects outweighs the benefits of improved analgesia. Despite the excellent analgesia afforded by use of intrathecal morphine, carefully controlled studies in high-risk patients have failed to demonstrate any beneficial effects on outcome in terms of reduced perioperative renal, pulmonary, and cardiac complications or mortality (21). The prolonged duration of action along with the risk of late respiratory depression associated with intrathecal morphine point to the need for hospitalization and monitoring after administration. This drug is not suitable for ambulatory procedures. Preservative-free morphine is currently the only drug discussed in this review that is approved by the United States Food and Drug Administration for intrathecal use in the treatment of acute pain.

### Other Opioids

**Fentanyl and Sufentanil**

Fentanyl and sufentanil are the best studied and most commonly used lipophilic drugs for intrathecal delivery. Two major trends in use of these drugs as analgesics have evolved in recent years: the first is a closer definition of their role as analgesics for labor, delivery, and postcesarean delivery; the second is the recognition that addition of small doses of lipophilic opioids during spinal anesthesia for ambulatory procedures can produce more rapid onset and better quality surgical block and lead to more rapid recovery of motor function and allow for earlier discharge after surgery. Both drugs can be summarized as having a rapid onset of analgesia (10–15 min) with a short duration of action (2–5 h).

Bucklin et al. (22) performed a meta-analysis of 7 randomized, controlled trials and concluded that intrathecal opioids (including morphine 200 μg, sufentanil 2-10 μg, and fentanyl 25 μg) provide comparable analgesia 15–20 min after injection in early labor with a more frequent incidence of pruritus compared with epidural local anesthetics. Duration of analgesia depends on the stage of labor. Viscomi et al. (23) found that 10 μg intrathecal sufentanil, combined with 2.5 mg of bupivacaine, provided analgesia that was significantly shorter in duration in advanced labor (120 ± 26 min) compared with early labor (163 ± 57 min). Intrathecal sufentanil is approximately 4.5 times more potent than intrathecal fentanyl in laboring parturients (24). Single-shot techniques provide predictable analgesia but of limited duration. In obstetrics, where prolonged labor and operative delivery often occur, many practitioners now take advantage of the best of both spinal and epidural techniques using combined spinal-epidural analgesia (CSE). In a prospective, randomized comparison of CSE versus epidural analgesia for labor, Norris et al. (25) found that progress and outcome of labor were similar in women receiving 10 μg intrathecal sufentanil with 2.0 mg bupivacaine or 10 μg epidural sufentanil and 12.5–25.0 mg bupivacaine followed by continuous epidural infusion of 0.083% bupivacaine plus 0.3 μg/mL sufentanil. Intrathecal opioids also provide effective analgesia after cesarean delivery. In a review of the use of intrathecal lipophilic opioids as adjuncts for surgical

### Table 1. Pharmacologic Properties of Common Opioids used for Intrathecal Analgesia

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Usual dose range (μg)</th>
<th>Onset (min)</th>
<th>Duration (h)</th>
<th>IT:IV potency ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>100–500</td>
<td>45–75</td>
<td>18–24</td>
<td>1:200</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5–25</td>
<td>5–10</td>
<td>1–4</td>
<td>1:10</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2.5–10</td>
<td>5–10</td>
<td>2–6</td>
<td>1:10</td>
</tr>
</tbody>
</table>

**Sufentanil**

Sufentanil 2.5–10 μg, 5–10 μg, 2–6 μg, 1:10

**Fentanyl**

Fentanyl 120 μg, 100 μg, 80 μg, 50 μg, 1:10

**Other Opioids**

**Opioid**

- **Morphine**
  - Usual dose range: 100–500 μg
  - Onset: 45–75 min
  - Duration: 18–24 h
  - IT:IV potency ratio: 1:200

- **Fentanyl**
  - Usual dose range: 5–25 μg
  - Onset: 5–10 min
  - Duration: 1–4 h
  - IT:IV potency ratio: 1:10

- **Sufentanil**
  - Usual dose range: 2.5–10 μg
  - Onset: 5–10 min
  - Duration: 2–6 h
  - IT:IV potency ratio: 1:10

**Table 2. The second generalization is that the incidence of side effects increases in proportion to the dose administered, with doses in excess of 300 μg producing nausea, vomiting, pruritus, and urinary retention in most recipients. Indeed, there appears to be a ceiling analgesic effect for intrathecal morphine above which the risk of side effects outweighs the benefits of improved analgesia. Despite the excellent analgesia afforded by use of intrathecal morphine, carefully controlled studies in high-risk patients have failed to demonstrate any beneficial effects on outcome in terms of reduced perioperative renal, pulmonary, and cardiac complications or mortality (21). The prolonged duration of action along with the risk of late respiratory depression associated with intrathecal morphine point to the need for hospitalization and monitoring after administration. This drug is not suitable for ambulatory procedures. Preservative-free morphine is currently the only drug discussed in this review that is approved by the United States Food and Drug Administration for intrathecal use in the treatment of acute pain.
spinal anesthesia, Hamber and Viscomi (18) recommended using 20–30 μg fentanyl or 5–7.5 μg of sufentanil to supplement bupivacaine spinal anesthesia for cesarean delivery. The addition of these doses of intrathecal opioid led to faster onset of block, improved intraoperative and postoperative analgesia that lasted 2.5–5 h, and decreased nausea and vomiting during cesarean delivery.

Much recent work has focused on the addition of intrathecal lipophilic opioids to local anesthetics during spinal anesthesia for brief outpatient surgery. In this setting, adding fentanyl or sufentanil to bupivacaine or lidocaine results in more rapid onset of block and improved analgesia, both intraoperatively and for the first several hours after surgery (18). In efforts to take advantage of the improved analgesia without motor blockade, a series of investigations have examined combining lipophilic opioids with small doses of local anesthetic. Ben-David et al. (26) reported that patients receiving 20 mg of 0.5% lidocaine in dextrose with 20 μg fentanyl for knee arthroscopy were ready for discharge an average of 45 min after placement of the spinal drugs (range, 28–180 min ). Likewise, addition of fentanyl (10 μg) to small doses of hyperbaric bupivacaine (5 mg) enhanced the quality and duration of sensory block without prolonging the intensity or duration of motor block in patients undergoing knee arthroscopy (27). The addition of intrathecal fentanyl (10–25 μg) to surgical spinal anesthetics hastens the onset of surgical anesthesia, enhances intraoperative analgesia, and provides several hours of postoperative analgesia without prolonging motor block or delaying discharge.

**Meperidine**

Meperidine produces a local anesthetic effect in addition to its properties as an opioid analgesic (28). It has been reported to provide similar surgical anesthesia for perineal and lower extremity surgery as the sole anesthetic compared to bupivacaine (29). The duration of sensory block after intrathecal administration of meperidine was 112 ± 19 min in those receiving 1.5 mg/kg compared with 79 ± 27 min in those receiving 1.2 mg/kg; respiratory depression within 5–50 min of administration, hypotension (>30% decline in systolic arterial blood pressure), nausea, and vomiting were all common side effects (30). The addition of meperidine 10 mg to intrathecal bupivacaine for cesarean delivery was associated with prolonged postoperative analgesia but with more frequent intraoperative nausea and vomiting (31). Another randomized trial examining use of intrathecal meperidine (15 or 25 mg) for CSE during labor was halted because of the frequent incidence of the nausea and vomiting associated with this drug (32). Adding small doses of meperidine (0.3 mg/kg) to spinal lidocaine also prolongs postoperative analgesia after transurethral resection of the prostate (33). Despite the theoretic appeal of meperidine as a drug that can provide both opioid and local anesthetic effects, it has gained limited popularity owing to the frequent association with

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**Table 2. Optimal Intrathecal (IT) Opioid Dose for Specific Surgical Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Optimal IT opioid and dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labor analgesia</td>
<td>Sufentanil 2.5–5 μg</td>
<td>Larger doses (&gt;7.5 μg) are associated with an increased incidence of fetal bradycardia (129). Fentanyl (10–40 μg) and sufentanil (10–15 μg) improve intraoperative analgesia but do not produce significant postoperative analgesia (15). These intrathecal lipophilic opioids speed onset of block and improve both intraoperative and immediate postoperative analgesia without prolonging motor block (18). This small dose of intrathecal morphine was equivalent to 100 μg after TURP (130). Although these doses of intrathecal morphine provide excellent analgesia after total hip arthroplasty they are inadequate for pain relief after total knee arthroplasty, reflecting the greater degree of pain reported by patients undergoing knee replacement (16). Lumbar intrathecal morphine improves pain relief and reduces but does not eliminate the need for supplemental IV opioid analgesics (131). Lumbar intrathecal morphine administered prior to elective cardiac surgery combined with remifentanil/desflurane anesthesia provided superior analgesia when compared to a sufentanil/desflurane anesthetic (132). Lumbar intrathecal morphine provided more intense analgesia than IV patient-controlled analgesia with morphine (21).</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>Morphine 100 μg</td>
<td></td>
</tr>
<tr>
<td>Outpatient procedures under spinal anesthesia (e.g., knee arthroscopy)</td>
<td>Fentanyl 10–25 μg</td>
<td></td>
</tr>
<tr>
<td>Transurethral resection of the prostate (TURP)</td>
<td>Morphine 50 μg</td>
<td></td>
</tr>
<tr>
<td>Major orthopedic surgery (e.g., total joint arthroplasty)</td>
<td>Morphine 200–300 μg</td>
<td></td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>Morphine 500 μg</td>
<td></td>
</tr>
<tr>
<td>Fast-track cardiac surgery</td>
<td>Morphine 500–600 μg (8 μg/kg)</td>
<td></td>
</tr>
<tr>
<td>Major abdominal/vascular surgery (e.g., open abdominal aortic aneurysm repair)</td>
<td>Morphine 500–600 μg</td>
<td></td>
</tr>
</tbody>
</table>
nausea and vomiting. Detailed dose-response studies examining analgesic effects at smaller intrathecal doses are not available.

Hydromorphone

Long-term, continuous infusion of hydromorphone was not associated with spinal cord toxicity in an animal model (34) and has gained popularity and acceptance as an alternative to morphine as an analgesic drug for treatment of chronic pain using continuous intrathecal drug delivery systems (35). Hydromorphone has also been used effectively as a neuraxial drug for continuous epidural analgesia after thoracotomy (36), prostatectomy (37), and spinal fusion (38). Liu et al. (37) randomized 16 patients who had undergone prostatectomy to receive hydromorphone via patient-controlled analgesia either via an epidural or an IV route and measured the effectiveness and dose requirements. Patients receiving hydromorphone via the IV route required twice as much hydromorphone as those receiving the same drug via an epidural route (approximately 2 \( \mu g \cdot kg^{-1} \cdot h^{-1} \) versus 4 \( \mu g \cdot kg^{-1} \cdot h^{-1} \) in the IV versus epidural groups, respectively, during hours 3–24 after surgery). There are only limited data on intrathecal dosing of hydromorphone in the acute setting. Drakeford et al. (39) randomized 60 patients undergoing total joint arthroplasty to receive either saline, morphine 500 \( \mu g \), or hydromorphone 2 \( \mu g/kg \) intrathecally. Both morphine and hydromorphone produced significantly better postoperative pain relief with similar incidence of side effects when compared with saline. Like morphine, systemic doses of hydromorphone required to produce similar analgesia after IV administration are several hundred times the doses required after intrathecal administration (40) and produce similar duration of analgesia and side effects. The limited available data suggest that intrathecal hydromorphone 50–100 \( \mu g \) produces analgesia and side effects similar to 100–200 \( \mu g \) of intrathecal morphine with similar side effects and duration of action.

Methadone

The d-enantiomer of methadone is a weak opioid with low affinity to the N-methyl-d-aspartate (NMDA) receptor, a class of receptors with potential analgesic effects. However, in the antinociceptive dose range, the NMDA antagonism does not appear to contribute to the mechanism of d-methadone analgesia (41). There are only limited, uncontrolled reports of use of intrathecal methadone for intrathecal use via continuous infusion for chronic pain (42) and acute postoperative pain (43).

Non-Opioids as Adjuvants and Analgesics for Intrathecal Use

Clonidine

Clonidine is a specific \( \alpha_2 \)-receptor agonist; \( \alpha_2 \)-receptors are present within both presynaptic and postsynaptic terminals of primary afferent nociceptive neurons within the dorsal horn of the spinal cord. Spinal \( \alpha_2 \)-receptor agonists alter pain transmission by binding presynaptically to nociceptive A\( \delta \) and C fiber terminals and reducing neurotransmitter release, and postsynaptically by hyperpolarizing second order neurons within the dorsal horn (44). Clonidine produces analgesia by activating \( \alpha_2 \)-receptors; direct intrathecal administration produces selective spinally-mediated analgesia (45,46). Spinal clonidine produces dose-dependent analgesia with hypotension, bradycardia and sedation; it is not associated with respiratory depression or pruritus (47).

Clonidine has demonstrated effects on reducing both nociceptive and neuropathic pain in experimental models and in clinical use. Eisenach et al. (48) used intradermal capsaicin-induced hyperalgesia to produce central hypersensitivity and allodynia and noxious heat to produce acute pain in a series of healthy volunteers. They found that 150 \( \mu g \) of clonidine administered intrathecally, but not IV, relieved pain and allodynia, supporting a spinal selective mechanism for analgesia. In a placebo-controlled, randomized study, patients with severe cancer pain despite large doses of opioids received epidural clonidine (30 \( \mu g/h \)) or placebo (49). Epidural clonidine provided significant pain relief, particularly in patients with neuropathic pain.

Reports on the use of intrathecal clonidine in the perioperative period are numerous and collectively point toward synergistic action with spinal local anesthetics (50) with less urinary retention than spinal morphine (51). Clonidine has been demonstrated in numerous studies to prolong sensory and motor block. Eisenach et al. (47) reviewed the use of clonidine for regional anesthesia in 1996. Their summary analysis of numerous studies found that clonidine 75–225 \( \mu g \) (average, 146 \( \mu g \)) added to spinal bupivacaine 13.75–15 mg prolonged sensory block from 2.5 to 3.7 h and motor block from 2.4 to 3.3 h (47). Clonidine intensifies the degree of sensory block, reduces tourniquet pain (52), and appears to prolong and intensify the effects of spinal local anesthetic by altering systemic absorption (53). The degree of sympatholysis and hypotension after typical spinal local anesthetic doses (e.g., 15 mg bupivacaine) is near maximal; thus, adding intrathecal clonidine results in no increased hypotension (47). Hemodynamic effects of clonidine after neuraxial administration begin within 30 min, reach maximum effect within 1–2 h, and last approximately 6–8 h after a single injection (47).
There are few studies examining clonidine in combination with intrathecal opioids. Sites et al. (54) found that combining intrathecal morphine (250 μg) with intrathecal clonidine (25 or 75 μg) reduced the need for supplemental analgesics and improved pain control after total knee arthroplasty. Side effects were similar with the exception that patients receiving clonidine had more hypotension during the first 6 h after surgery.

Neostigmine

Spinal administration of neostigmine, an acetylcholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia (50). Eisenach et al. (55) demonstrated that acetylcholine has intrinsic analgesic properties, and that the concentration of acetylcholine in CSF is increased during painful electrical stimulation. They further suggested that enhanced amounts of acetylcholine released from preganglionic sympathetic neurons after spinal neostigmine administration may counteract the sympatholytic actions of local anesthetics or α2-agonists (reducing the degree of hypotension) and add a synergistic antinociceptive effect to spinal α2-agonists (55).

In preliminary dose-ranging studies in surgical patients and healthy volunteers, intrathecal neostigmine 10–50 μg provided analgesia (56). Nausea and lower extremity weakness were common in doses exceeding 100–150 μg, but sedation, pruritus, respiratory depression, and hemodynamic changes did not occur (57). Adding 6.25–25 μg neostigmine to spinal bupivacaine improves sensory and motor block (56), delays resolution of block (56), and reduces postoperative analgesic requirements (58). All doses were associated with a frequent incidence of nausea and vomiting that was resistant to pharmacologic treatment (56,58).

One study (59) demonstrated that adding 1–5-μg neostigmine to 100 μg intrathecal morphine improved analgesia without increasing side effects after gynecological surgery. The incidence of nausea and the prolongation of recovery from spinal anesthesia suggest that neostigmine is not a useful adjuvant; further examination of small dose neostigmine in combination with intrathecal opioids is warranted.

Adenosine

Adenosine produces receptor-specific analgesia via both peripheral and central mechanisms, and adenosine receptors are present in high density within the dorsal horn of the spinal cord (60). After animal toxicity testing suggested safety, a phase I dose-ranging trial of 0.25–2 mg of intrathecal adenosine in healthy volunteers showed no effect on arterial blood pressure, end-tidal carbon dioxide, or neurologic function; headache and back pain were common side effects (61). Adenosine produced no effect on acute thermal or chemical pain but reduced mechanical hyperalgesia and allodynia from intradermal capsaicin for at least 24 h (62). Adenosine concentrations in CSF increased after intrathecal, but not IV, administration of opioids, suggesting a role for adenosine in spinal opioid receptor activation and analgesia (63). A randomized study of 25 parturients who received 10 μg of intrathecal sufentanil with or without 500 μg of adenosine showed no differences in the degree or duration of pain relief (64). Further clinical trials of intrathecal adenosine are warranted; its role as an analgesic will likely be limited to injury associated with acute hyperalgesia (e.g., surgery) and treatment of neuropathic pain (62).

Epinephrine

Adding the vasoconstrictor epinephrine (0.1–0.6 mg) to spinal local anesthetics intensifies and extends the duration of sensory and motor block in a dose-dependent fashion (65,66). Epinephrine may produce both direct analgesia through α-adrenergic receptor binding as well as prolongation of local anesthetic effect by vasoconstriction and decreased intensity of clonidine (74). Further study is needed to define the role of α2 agonists in spinal anesthesia. The expense of delayed return of motor function and micturition (69).

Ketorolac

Cyclooxygenase-2 (COX-2) activity in the spinal cord plays a key role in sensitization to sensory stimuli during acute inflammation (70), but intrathecal administration of COX-2 specific inhibitors has minimal analgesic effects in an incisional model of postoperative pain (71). Studies in experimental animals suggest that COX-1 plays an important role in spinal cord pain processing and sensitization after surgery and that spinally administered specific COX-1 inhibitors may be useful to treat postoperative pain (72). In a phase I safety assessment of intrathecal ketorolac in volunteers, a single 0.25–2 mg intrathecal dose of ketorolac did not affect sensory or motor function or deep tendon reflexes, and there were no subjective sensations, neurologic or otherwise, reported by the volunteers. Ketorolac did not reduce pain reported from heat stimuli applied to the lateral calf (73). Intrathecal ketorolac lacks efficacy in normal rats subjected to acute, noxious heat stimuli but enhances the antinociceptive effects of clonidine (74). Further study is
needed to define the role of intrathecal ketorolac in treating acute pain.

**Midazolam**

There has been much recent attention toward the use of the benzodiazepine midazolam as an intrathecal drug in the treatment of both acute and chronic pain. Yaksh and Allen (75) recently reviewed the existing animal and human data regarding use of intrathecal midazolam. Basic science work with γ-amino butyric acid suggests that it may play an important role in regulating primary as well as dorsal (sensory) and motor horn excitability. Preclinical studies in animal models have demonstrated significant analgesia without changes in sympathetic outflow. At larger doses (typically 3 or more times the dose required to produce analgesic effects), reversible degradation of motor strength and coordination appear. Early toxicity studies in rabbits (76) suggested that midazolam produced significant spinal cord toxicity, even after single-shot administration in clinically relevant doses. However, recent animal studies examining the effects of long-term intrathecal administration of midazolam showed no discernible toxicity (77). Yaksh and Allen (75) conclude that current data “...support the assertion of a degree of safety for this modality [intrathecal midazolam] within the doses and concentrations examined.”

The use of intrathecal midazolam in humans has been reported in at least 18 peer-reviewed reports with an estimated 797 patients (75) since 1986. The overall clinical effects are characterized by an increased duration of sensory and motor block when administered with spinal local anesthetic, an increase in time to first request for supplemental analgesia postoperatively, and a decrease in postoperative analgesic requirements. There appears to be no increase in adverse effects, including hypotension, bradycardia, micturition, or nausea/vomiting, when midazolam is combined with another intrathecal local anesthetic and/or opioid compared with groups not receiving intrathecal midazolam. Tucker et al. (78) reported a prospective observational study of 1100 patients who underwent various surgical procedures with spinal anesthesia with or without the addition of 2 mg of intrathecal midazolam. Intrathecal midazolam was not associated with an increased risk of symptoms suggestive of neurological impairment, including motor or sensory changes and bladder or bowel dysfunction. Tucker et al. (79) randomized 30 parturients to receive intrathecal midazolam 2 mg, fentanyl 10 μg, or the combination of both drugs. Labor pain was not altered by midazolam alone, was modestly reduced by fentanyl alone, and was reduced most by the combination of the two drugs. They concluded that intrathecal midazolam enhanced the analgesic effect of fentanyl without increasing maternal or fetal adverse effects. Current reports suggest that the use of midazolam in a dose not exceeding 1–2 mg at a concentration not exceeding 1 mg/mL, delivered either alone or as an intrathecal adjuvant, has positive effects on perioperative pain and does not increase the incidence of adverse events (75). Although current formulations are preservative-free, commercially available stock solutions of midazolam hydrochloride are supplied in concentrations of 5 mg/mL at pH 3.4–3.6 (75). The solubility rapidly declines to <1 mg/mL at pH 4.5–5, and cloudiness (precipitation) has been reported when the 5 mg/mL is diluted with higher pH saline or CSF (80).

**Complications Associated with Intrathecal Opioid Use**

**Pruritus**

Pruritus after intrathecal administration of opioids is common and occurs more often than after systemic administration. Szarvas et al. (81) reviewed the pathophysiology and treatment of neuraxial opioid-induced pruritus. The incidence of pruritus after intrathecal administration of opioid varies from 30% to 100% (82–87). The incidence among the commonly used intrathecal opioids (morphine, fentanyl, sufentanil) has been reported to be similarly frequent (88,89). The exact mechanism of neuraxial opioid-induced pruritus remains unclear (83). Naloxone’s reversibility of pruritus supports the existence of an opioid receptor-mediated central mechanism. The mechanism does not appear to be histamine related (90). Pharmacological therapies include antihistamines, 5-HT₃-receptor antagonists, opiate antagonists and combination agonist-antagonists, propofol, and nonsteroidal anti-inflammatory drugs (83). Histamine is not released and does not appear to be causative (91). Antihistamines are thus unlikely to have any role in prevention. The sedative properties may be helpful in interrupting the itch-scratch cycle but without relieving itch sensation (92). Despite its widespread use, diphenhydramine has little demonstrated efficacy in the treatment of neuraxial opioid-induced pruritus (84,90). Ondansetron has demonstrated efficacy in both prevention and treatment of pruritus associated with neuraxial opioids (84,93). The opioid antagonists naloxone and naltrexone (91), as well as the agonist-antagonist nalbuphine (94), are the most effective drugs for prevention and treatment of neuraxial opioid-induced pruritus. When the pure antagonists are used in larger doses, they also reverse analgesia (94). Nalbuphine appears to be the most effective drug when compared with naloxone, diphenhydramine, and ondansetron (94,95). Propofol, in subhypnotic doses, has also proven effective in the prevention and treatment of...
neuraxial opioid-induced pruritus. Propofol, 10 mg bolus followed by 30 mg/24h infusion (96) or 10 mg without infusion (97), markedly reduced the incidence of pruritus. However, studies in obstetric populations have failed to show any effect of similar doses of propofol on neuraxial opioid-induced pruritus (98,99). Treatment of opioid-induced pruritus remains a challenge. Ondansetron, propofol, and nalbuphine have proven efficacy in the treatment of neuraxial opioid-induced pruritus (Table 3).

Urinary Retention

Urinary retention after administration of intrathecal opioids is common. This side effect can be observed soon after intrathecal injection of morphine and lasts for 14–16 h, regardless of the dose used (100). The incidence of urinary retention appears to be most frequent with intrathecal morphine at ~35% (101) and is more common after neuraxial administration than after IV or IM administration (102). The incidence does not appear to be dose related but is more frequent after intrathecal morphine than after lipophilic opioids (103,27). Indeed, intrathecal sufentanil alone for lithotripsy was associated with a shorter time to voluntary micturition than spinal lidocaine (104). Opioids affect urination via several mechanisms including alteration of parasympathetic tone and central analgesic action, which modify the pain threshold for the bladder and contribute to retention (100). Urinary retention secondary to neuraxial opioids is likely related to interaction with opioid receptors located in the sacral spinal cord. This interaction promotes inhibition of sacral parasympathetic nervous system outflow, which causes marked detrusor muscle relaxation and an increase in maximal bladder capacity (100). Naloxone can prevent or reverse urodynamic changes after neuraxial morphine; however the dose required may partially or completely reverse analgesia (100). Nalbuphine may also reverse the urinary effects of neuraxial morphine (105). If patients are unable to void for ≥6 h, urinary catheterization should be performed to prevent myogenic bladder damage resulting from prolonged distention. Because urinary retention is infrequent with use of lipophilic intrathecal opioids, they are the preferred adjuvants for outpatient surgery with spinal anesthesia (18).

Nausea and Vomiting

All opioids, regardless of route of administration, can produce nausea and vomiting. The incidence after neuraxial administration is approximately 30% (106), but the incidence varies with the particular opioid used and, in some settings, also varies with the dose administered. Intrathecal morphine led to a dose-dependent increase in vomiting in volunteers (15) but caused no increase in nausea and vomiting when added to spinal bupivacaine (107,108). Others have demonstrated a dose-dependent increase in nausea and vomiting with intrathecal morphine (109,110). Together, these data suggest that intrathecal morphine does not increase the incidence of nausea and vomiting after major surgery when compared with systemic administration of morphine, particularly if the dose is <100 µg (111). In contrast, fentanyl and sufentanil have been associated with little or no nausea or vomiting after intrathecal administration of a single dose (103,112,113).

Nausea and vomiting induced by neuraxial opioids may be a systemic effect, particularly with lipophilic opioids, or may be the result of cephalad migration of drug in the CSF and subsequent interaction with opioid receptors located in the area postrema (111). Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may also play a role.

For shorter or less painful procedures, use of lipophilic opioids will minimize the risk of nausea and vomiting. Both fentanyl and sufentanil were shown to decrease the rate of intraoperative nausea and vomiting during cesarean delivery when compared with local anesthetic alone for spinal anesthesia (18). Dexamethasone and droperidol have been shown to be effective for prevention of nausea and vomiting after epidural morphine (114). Combinations of scopolamine and promethazine used as preventative measures decreased the incidence of nausea and vomiting (111).

Respiratory Depression

The most feared complication of opioid administration is respiratory depression. The pharmacology and time course of opioid-induced respiratory depression have been discussed previously in this review (Fig. 2). The true incidence of clinically significant respiratory depression is not known, but evidence from smaller controlled trials and large observational studies confirm that it is infrequent (115). The majority of prospective studies of epidural morphine have not detected clinically significant respiratory depression, but they are hindered by relatively small sample sizes and are markedly underpowered to detect such a rare event (116). Ko et al. (117) reviewed the use of the term “respiratory depression” and found that there is no clear definition, leading to difficulty and confusion when comparing available studies. The incidence is infrequent for doses commonly used clinically but the incidence is dose-dependent for both hydrophilic and lipophilic opioids (118). The incidence of respiratory depression associated with continuous epidural infusions containing opioids has been estimated from large observational studies, with estimates ranging from 0.09% to 0.4% (119–125). The risk of respiratory
### Table 3. Incidence, Proposed Mechanisms, and Treatment for Intrathecal Opioid-Related Side Effects

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
<th>Proposed mechanism</th>
<th>Treatment</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>• Varies from 30%–100%</td>
<td>Exact mechanism unclear. Postulates include “itch center” in the central nervous system, medullary dorsal horn activation, antagonism of inhibitory transmitters. Modulation of the serotonergic pathway and involvement of prostaglandins may be important as well.</td>
<td>• Ondansetron 4–8 mg IV</td>
<td>• Propofol may be less effective for the parturient</td>
</tr>
<tr>
<td></td>
<td>• Increased in parturients</td>
<td></td>
<td>• Nalbuphine 4 mg IV</td>
<td>• Histamine release does not appear to be causative</td>
</tr>
<tr>
<td></td>
<td>• Varies with opioid used</td>
<td></td>
<td>• Propofol 10 mg IV bolus + small dose infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Likely dose dependent</td>
<td></td>
<td>• Infusion of naloxone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased with epinephrine</td>
<td></td>
<td>• Oral naltrexone</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>• As frequent as 35% with morphine</td>
<td>Likely related to interaction with opioid receptors in the sacral spinal cord, promoting inhibition of sacral parasympathetic nervous system outflow. This causes detrusor muscle relaxation and an increase in maximal bladder capacity.</td>
<td>• Opioid antagonist and agonist-antagonist including naloxone, naltrexone and nalbuphine</td>
<td>• Inability to void postoperatively is a multifactorial problem—risk factors include surgery type (especially hernia), preexisting obstructive problems, volume status, spinal anesthesia with epinephrine.</td>
</tr>
<tr>
<td></td>
<td>• More common than with IV/IM administration</td>
<td></td>
<td></td>
<td>• This is μ- and δ-receptor mediated</td>
</tr>
<tr>
<td></td>
<td>• Morphine &gt; fentanyl/sufentanil</td>
<td></td>
<td></td>
<td>• Intrathecal opioids appear to have a protective effect against intraoperative nausea and vomiting during cesarean delivery</td>
</tr>
<tr>
<td></td>
<td>• Not dose related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>• Different rates for different opioids (morphine &gt; fentanyl = sufentanil)</td>
<td>May be a systemic effect vs. cephalad migration in the cerebrospinal fluid (CSF) and interaction with opioid receptors in the area postrema. Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may play a role.</td>
<td>• Use smallest effective dose</td>
<td>• Inability to void postoperatively is a multifactorial problem—risk factors include surgery type (especially hernia), preexisting obstructive problems, volume status, spinal anesthesia with epinephrine.</td>
</tr>
<tr>
<td></td>
<td>• Likely dose dependent</td>
<td></td>
<td>• For ambulatory procedures use lipophilic opioid instead of morphine.</td>
<td>• This is μ- and δ-receptor mediated</td>
</tr>
<tr>
<td></td>
<td>• Frequent incidence with IV/IM</td>
<td></td>
<td>• Dexmedetomidine and droperidol have shown efficacy as well as combinations of scopolamine and promethazine.</td>
<td>• Intrathecal opioids appear to have a protective effect against intraoperative nausea and vomiting during cesarean delivery</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>• Overall estimates: 0.07%–0.49%.</td>
<td>Secondary to rostral spread in CSF</td>
<td>• Opioid antagonists including naloxone, naltrexone, nalbuphine</td>
<td>• Risk factors include large dose; concomitant use of additional opioid and or sedatives, age &gt;65 yr, opioid naïve patient</td>
</tr>
<tr>
<td></td>
<td>• Dose dependent</td>
<td></td>
<td></td>
<td>• Late onset depression more apparent with morphine</td>
</tr>
<tr>
<td></td>
<td>• All opioids can cause</td>
<td></td>
<td></td>
<td>• There is not an opioid free from risk</td>
</tr>
<tr>
<td></td>
<td>• Typically lipophilic early onset (&lt;2 h) and morphine both early and late onset (6–12 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
depression after epidural or intrathecal opioid is less than 1%, and limited data suggest that the risk is similar to that of opioids delivered via the parenteral route (116). In a double-blind study of healthy volunteers randomly assigned to receive placebo, IV morphine (0.14 mg/kg), or intrathecal morphine (300 μg), depression of the ventilatory response to hypoxia was similar in magnitude after either IV or intrathecal morphine but longer lasting after intrathecal administration (126).

Risk factors for the development of respiratory depression include large doses, concomitant use of additional opioids and/or sedatives, administration in opioid-naive patients, and age >65 yr (116,122,123). Detection of respiratory depression after intrathecal administration of opioid may be difficult. Respiratory rate may or may not decrease (124), and significant hypercapnia can occur despite a normal respiratory rate (124). Pulse oximetry may be valuable (15), but the most reliable clinical sign of significant respiratory depression appears to be a depressed level of consciousness (116,124). Protocols for monitoring vary, but typical duration of monitoring is 18 to 24 h after intrathecal morphine and 4 to 6 h after intrathecal fentanyl or sufentanil (124). Lipophilic opioids are now used more frequently in the ambulatory setting, where patients are discharged shortly after surgery; respiratory depression more than 2 h after intrathecal injection of fentanyl or sufentanil has never been described. Patients can be safely managed on regular wards when personnel are trained, emergency guidelines are available, patient dosing and selection are appropriate, and respiratory rate and patient level of consciousness are checked hourly (124). The efficacy and safety of spinal opioids in surgical wards are best assured when these analgesic techniques are used under the supervision of organized acute pain services (127,128).

Conclusions

Intrathecal administration of opioids can provide excellent pain relief after a wide range of operative procedures, including procedures performed in the ambulatory setting. Understanding of optimal doses for specific procedures has improved, but side effects remain common. Knowledge of spinally mediated analgesia is evolving rapidly and a number of non-opioid compounds may prove useful as analgesics that will reduce side effects and improve treatment for both nociceptive and neuropathic pain.

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Audit of motor weakness and premature catheter dislodgement after epidural analgesia in major abdominal surgery

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Summary

In a quality improvement audit on epidural analgesia in 300 patients after major abdominal surgery, we identified postoperative lower leg weakness and premature catheter dislodgement as the most frequent causes of premature discontinuation of postoperative epidural infusion. Lower limb motor weakness occurred in more than half of the patients with lumbar epidural analgesia. In a second period monitoring 177 patients, lumbar catheter insertion was abandoned in favour of exclusive thoracic placement for epidural catheters. Additionally, to prevent outward movement, the catheters were inserted deeper into the epidural space (mean (SD) 5.2 (1.5) cm in Period Two vs 4.6 (1.3) cm in Period One). Lower leg motor weakness declined from 14.7% to 5.1% (odds ratio 0.35; 95% confidence interval 0.16–0.74) between the two periods. Similarly, the frequency of premature catheter dislodgement was reduced from 14.5% to 5.7% (odds ratio 0.35; 95% confidence interval 0.17–0.72). With a stepwise logistic regression model we demonstrated that the odds of premature catheter dislodgement was reduced by 43% for each centimetre of additional catheter advancement in Period Two. We conclude that careful audit of specific complications can usefully guide changes in practice that improve success of epidural analgesia regimens.

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Peri-operative analgesic protocols that include a combination of general and epidural analgesia have been introduced for a wide variety of surgical procedures to reduce stress response and allow immediate postoperative rehabilitation [1, 2]. Epidural analgesia significantly reduces the incidence of cardiovascular events, acute respiratory failure, deep venous thrombosis and gastrointestinal paralysis after major abdominal surgery [3, 4]. Therefore, it is important to maximise efficacy of postoperative epidural analgesia. Up to 15% of postoperative epidural analgesia failures are due to technical problems leading to premature dislodgement of the catheter or disconnection of the infusion. Failures due to inadequate analgesia despite properly-functioning catheters account for another 8–12% [5–7]. Such failures cause patient discomfort and delays in the rehabilitation process.

Audits have proved generally useful in maintaining standards of care and might be useful in identifying problems with postoperative epidural therapy, especially those important in the setting of a local unit. We conducted an audit of postoperative epidural analgesia in our unit by first identifying common causes for our postoperative epidural failures, then initiating new standards and finally monitoring the success of these interventions.

Methods

This project was undertaken to improve the quality of epidural analgesia in our unit. The Ethics Committee of the University Hospital Tübingen approved the conduct of this audit and publication of its results.

The audit was organised in two parts.
Period One

First, to identify the main reasons for premature cessation of postoperative epidural analgesia, we retrospectively analyzed the data of 300 patients in whom epidural analgesia had been used after major abdominal surgery in the Department of General, Visceral, and Transplantation Surgery over a 13-month period.

Conduct of epidural analgesia and anaesthesia

Our local policy is that exclusion criteria for pre-operative catheter placement are: patient refusal, coagulation disorders, signs of local or systemic infection, and anatomical abnormalities. Our standard hospital protocol involves identifying the epidural space with the patient sitting upright, using a midline approach and the loss-of-resistance technique to either air or saline. It was our local policy that either the lumbar or thoracic vertebral interspace was selected for epidural catheter placement on the basis of the dermatomal extent of the surgical procedure and skin incision. Thus, patients scheduled for colorectal surgery or surgery in the lower pelvic region received lumbar epidural analgesia, while higher surgical incisions received thoracic epidural analgesia. The catheter is routinely affixed to the skin at the insertion site with a dressing consisting of steri-strips™ (3M Health Care, St Paul, MN, USA), a porous tape with a small hole in oxygen. According to local guidelines, the patients received an epidural loading dose of ropivacaine 45 mg and sufentanil (0.2 μg.kg⁻¹) and maintained with sevoflurane in oxygen/air. According to local guidelines, the patients received an epidural loading dose of ropivacaine 45 mg and sufentanil 10 μg followed by continuous epidural infusion of ropivacaine 30 mg.h⁻¹ and sufentanil 3 μg.h⁻¹. Postoperatively, continuous infusion was reduced to ropivacaine 12 mg.h⁻¹ and sufentanil 3 μg.h⁻¹ and then titrated according to presence of pain and sensory block. Additionally, paracetamol 4 g.24 h⁻¹ or metamizole up to 5 g.24 h⁻¹ were prescribed.

Postoperative care and data collection

Postoperatively, patients with epidural catheters were assigned to the care of an acute postoperative pain service team. A tracking sheet was initiated by the anaesthesiologist inserting the epidural catheter. The sheet contained data on catheter placement, patient demographics, and prescribed epidural drug infusion. Patients were visited twice daily on the ward by a member of the acute pain service team. The ‘tracking’ sheet recorded the following: vital parameters, presence of absence of pain, motor weakness (modified Bromage scale: 0 = free movement of legs; 1 = knee flexion barely possible-foot lifting unconfined; 2 = knee flexion impossible-foot lifting barely possible; 3 = no movement possible), paraesthesia (i.e. prickling sensations in the lower limbs or body), the details of the prescribed epidural drug infusion, and any free-text notes. Motor weakness of the legs was defined as a Bromage score > 0. We classified ‘insufficient analgesia’ as any state in which unilateral distribution of the epidural block, or pain as reported on the tracking sheet. The catheter insertion site was inspected once per day. According to hospital protocol, the continuous infusion was stopped no sooner than the fourth postoperative day or after postoperative ileus had resolved (with the final decision left to the discretion of the responsible attending anaesthetist). The epidural catheter was removed when the tracking sheet confirmed the patient was pain-free.

Period Two

Following the review of the data of Period One, we changed certain policies and (a) limited catheter placement to thoracic interspaces T8-11, (b) stipulated that catheters be advanced 1 cm deeper into the epidural space. Thus, practitioners who had placed their catheters 4 cm into the epidural space in Period One were instructed to advance them at least 5 cm deep; those who had placed their catheters 5 cm deep were instructed to advance them now 6 cm (with an absolute upper limit in the new guidelines of 6 cm). The remainder of the protocols for conduct of analgesia and anaesthesia were unchanged. During this second period 177 patients received an epidural catheter.

Statistical analysis

Variables are given as mean (SD), median [interquartile range] or as frequency, as appropriate. Significance of the differences between the groups was evaluated by univariate comparisons: analysis of variance for continuous variables and chi-squared tests for discrete data. Nonparametric tests (Wilcoxon, Kruskal–Wallis) were used where distributions were extremely skewed. Odds ratios (OR) and estimated 95% confidence intervals (CI) for single risk factors were stratified by time period. For quantitative variables the OR per unit, e.g. for one additional centimetre of catheter advancement, was estimated by logistic regression. We used a stepwise variable selection to find a model that described the main factors involved in an adjusted manner. Calculations were done with JMP 7.0 [8].

Results

Patient characteristics are listed in Table 1 and suggest similar populations between the two time periods. The
mean duration of catheter placement and the nature of the surgery performed did not differ significantly between Period One and Period Two.

In Period One, 19.7% of the epidural catheters were placed in a lumbar intervertebral space and 80.3% in a thoracic intervertebral space (Fig. 1). A review of the database identified postoperative lower limb motor weakness as the most frequently noted abnormality taken care of by the acute pain service team (14.7%) (Table 2): 52.4% of patients with epidural catheters placed in a lumbar intervertebral space developed postoperative motor weakness of the legs, compared with only 4.8% of patients with a thoracic epidural catheter.

Following the change in policy to thoracic placement only (2.3% of epidural catheters were nonetheless inserted into a lumbar intervertebral space) there was a significant reduction in postoperative lower limb motor weakness (5.1% vs 14.7%; OR 0.35; 95% CI 0.16–0.74). The percentage of patients with inadequate postoperative analgesia remained unchanged (10.3% vs 12.2%; OR 0.82; 95% CI 0.45–1.51).

Following the change to deeper catheter placement, we found epidural catheters inserted 5.2 (1.5) cm in Period Two vs 4.6 (1.3) cm in Period One. As a result, the rate of catheter dislodgement was significantly reduced (5.1% vs 14.7%; OR 0.35; 95% CI 0.17 to 0.72). We further calculated by linear regression that the OR for catheter dislodgement was reduced by 43% for every cm of additional catheter advancement into the epidural space (unit OR 0.57; 95% CI 0.34–0.93) within Period Two. The frequency of catheter dislodgement was independent of gender, body mass index, age, site of insertion (thoracic or lumbar), ASA status, or type of surgery.

Discussion

This quality improvement audit achieved a significant reduction of postoperative leg weakness and premature catheter dislodgement in patients by promoting the near-exclusive use of thoracic placement of epidural catheters and by inserting the catheters deeper into the epidural space.

The use of epidural analgesia for intra- and postoperative pain control has become an important element of early rehabilitation programs. The occurrence of lower limb motor weakness frequently impedes patient mobilization and leads to transient discontinuation of epidural analgesics, increasing patient discomfort. This impairment of motor function results from the anaesthesia of the lumbar and sacral plexuses. It has been shown that after epidural application, the highest concentrations of local anaesthetic agents are found in the spinal roots and pia arachnoid. Significant amounts of local anaesthetic are demonstrated in the peripheral parts of the spinal cord. Additionally, diffusion of the drugs along the spinal roots

Table 1 Patient characteristics, duration of epidural catheter placement, and surgery details. Values are median [interquartile (IQ) range], mean (SD) or number (proportion) as indicated.

<table>
<thead>
<tr>
<th></th>
<th>Period One (n = 300)</th>
<th>Period Two (n = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>59 (13)</td>
<td>60 (14)</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>165 : 132</td>
<td>106 : 71</td>
</tr>
<tr>
<td>BMI; kg.m⁻²</td>
<td>25.8 (6.3)</td>
<td>25.1 (5.7)</td>
</tr>
<tr>
<td>ASA; I:II:III (%)</td>
<td>7 : 72 : 21</td>
<td>8 : 64 : 26</td>
</tr>
<tr>
<td>Catheter duration:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoraco-abdominal surgery (%)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Upper abdominal surgery (%)</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Colorectal surgery (%)</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Miscellaneous surgery (%)</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

BMI, Body mass index; ASA, American Society of Anesthesiology.

Table 2 Site and failure rate (by motor weakness and dislodgement of catheter) of epidural. Values are mean (SD) or number (proportion). CI, confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>Period One (n = 300)</th>
<th>Period Two (n = 177)</th>
<th>Odds ratio [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic/lumbar site; n</td>
<td>241 : 59</td>
<td>173 : 4</td>
<td>0.11 [0.04–0.33]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lumbar epidural; %</td>
<td>19.7</td>
<td>2.3</td>
<td>0.11 [0.04–0.33]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Motor weakness; %</td>
<td>14.7</td>
<td>5.1</td>
<td>0.35 [0.16–0.74]</td>
<td>0.0013</td>
</tr>
<tr>
<td>Catheter dislodgement; %</td>
<td>14.5</td>
<td>5.7</td>
<td>0.35 [0.17–0.72]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Epidural catheter depth; cm</td>
<td>4.6 (1.3)</td>
<td>5.2 (1.5)</td>
<td>0.79 [0.64–0.98]</td>
<td>0.004</td>
</tr>
<tr>
<td>Insufficient analgesia; %</td>
<td>12.2</td>
<td>10.3</td>
<td>0.82 [0.45–1.51]</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Figure 1 Monthly postoperative epidural catheter case load (black line: thoracic epidural catheters, grey line: lumbar epidural catheters) during Period One (13 months) and Period Two (7 months).
into the cerebrospinal fluid and the spinal cord might affect the two major descending motor pathways that run downwards superficially at lumbar levels [9–11]. In contrast, it is unclear whether drug penetration is deep enough to affect a significant proportion of ascending and descending tracts and contribute to leg weakness when local analgesics are injected at thoracic levels [11]. Our results are consistent with those of previous studies reporting a rate of leg motor impairment between 40% and 50% in patients after lumbar epidural analgesia [12].

In our Period One, lumbar epidural analgesia was preferred at our institution in patients scheduled for lower pelvic and colorectal surgery. The rationale for catheter insertion site was that the intervertebral segments of the affected splanchnic nerves of the inferior mesenteric plexus (L1–L2) are stimulated by lesser pelvis, left colon, sigmoid, and rectal surgery as well as the dermatomal segments of the laparotomy incision. Additionally, it seemed reasonable to assume that the danger of direct nerve damage would be lower with lumbar needle insertion than it would for thoracic needle insertion (although we are not aware of published data to substantiate this).

To reduce the rate of leg motor weakness in Period Two we considered two possible treatment changes. First, we could have confined the catheter insertion site to thoracic levels (based on the considerations above), or second we could have used lower doses of local anaesthetics. However, the latter might have led to insufficient analgesia [13]. Since we were already using a reasonably low dose of ropivacaine with an opioid, which has been recommended as an effective postoperative analgesic after abdominal surgery [13–15], we chose not to reduce local anaesthetic concentrations further but instead change the insertion sites to thoracic level. Our results suggest that thoracic epidural analgesia was as successful as lumbar epidural analgesia [9, 16].

While our rate of premature catheter dislodgement (14.5%) during Period One may seem high, comparable rates are reported by others [6, 17–19]. We considered this unacceptably high, as it hampered postoperative rehabilitation and was unpleasant for the patients if a new catheter placement became necessary. Our intention in advancing the catheter insertion deeper was to establish a broader margin for outward catheter mobility during patient mobilization. One reason for premature catheter dislodgement is fluid leakage along the outside of the catheter into the muscles of the back or to the skin [19]. The fluid can accumulate under the adhesive dressing and loosen the tape fixation to the skin [20]. Towards its tip, the catheter is usually gripped tightly by the ligamentum flavum. Due to the presence of a midline septum or postsurgical adhesions the reduced capacity of the epidural space is easily filled and then a retrograde flow of epidural solutions could loosen the grip [21]. Moreover, 30–40% of catheters which are properly placed initially have been shown to move outwards within the epidural space over time [22]. Consequently, increasing frequency of dislodgement over the duration of catheterization has been shown [23, 24]. However, we examined neither the duration of catheterization before dislodgement nor the rate of fluid leakage so the main reasons for premature dislodgement in our study remain unclear.

In a study of epidural analgesia during labour, catheter insertion to a depth of 7 cm was associated with the highest rate of insertion complications, while insertion to a depth of 5 cm was associated with the highest incidence of satisfactory analgesia [25]. Therefore, we limited the catheter insertion depth to 5–6 cm. Subcutaneous tunnelling and suture techniques have been used to prevent outward movement of epidural catheters [22], but are somewhat invasive and time-consuming. Others have recommended using an ‘epidural catheter clamp’ to reduce rates of premature catheter dislodgements from 16% to 4% [17] but we achieved the same effect by simply advancing the catheter deeper into the epidural space. We were, though, surprised that a relatively small change in insertion depth of < 1 cm had such a beneficial effect on dislodgement.

Our study does have some limitations. While we could demonstrate a significant reduction of leg motor weakness and unintentional catheter dislodgements, no data were collected on end-points such as reduced morbidity, time to discharge or reduction of the number of unscheduled patient visits by the members of the postoperative pain service team. Moreover, this is not an interventional study but an audit. Generally, results may have been confounded by seasonal variation, the fact the staff were aware of the audit (i.e. no blinding), staff changes, and other aspects that we could not control as we might in a formal study. The data analysis for time Period One was limited to 13 months. During this time span, a full data set was available, and no changes in the peri-operative management occurred. Time Period Two was much shorter and ended after 7 months because – independent of this audit – there was a change of the general anaesthesia induction protocol. We did not think it correct to include this subsequent data in this audit. While we assessed occurrence of pain by it being noted on our tracking charts, we did not use a formal visual analogue scale so our assessment of this important variable is a shortcoming. Thus, while we demonstrate improvements in quality of motor weakness and catheter dislodgement rates, we cannot show that this is translated into any benefit in pain control. Nonetheless we can be confident that there was unlikely to have been a significant increase.
in this measure as a result of the changes we introduced (Table 2).

In summary, future audits or studies will extend to cover other surgical disciplines where postoperative lumbar epidural analgesia is frequent, e.g. urology or gynaecology. We feel that our rate of ~6% for premature catheter dislodgement remains unacceptably high and there is room for improvement. Studies assessing combinations of methods to further reduce this rate (e.g. fixation methods, epidural catheter clamp, and catheter advancement) are desirable.

References
Spinal anaesthesia: a century of refinement, and failure is still an option

On August 24, 1898, August Bier and his assistant Hildebrandt undertook ‘experiments on [their] own bodies’ which were part of their historic initial investigations of spinal anaesthesia. Bier’s description of these experiments is notable for the manner in which he documented the lack of sensibility after injection of cocaine into Hildebrandt’s subarachnoid space, which included a burning cigar, a strong blow to the shin with an iron hammer, and strong pressure and traction on the testicles, none of which provoked pain. Absent from this report are descriptions of similar assessments being performed by Hildebrandt on Bier. This was not out of deference to Bier, but rather the Pravaz syringe failed to fit on the needle, and a significant amount of the cocaine intended for Bier’s subarachnoid space was lost, resulting in a failed block.

Although the aetiology of this historic failure is no mystery, a particularly perplexing and frustrating problem with spinal anaesthesia is the occasional failure to achieve adequate sensory block, despite an apparently orthodox injection of an adequate dose of local anaesthetic. Believing certain subjects to be ‘hyper-resistant’ to spinal anaesthesia, Sebrechts coined the term ‘rachi-resistance’ in 1934 to describe this phenomenon. He postulated that this aberration reflected a ‘peculiar idiosyncrasy which renders the nerve roots of certain individuals insensitive or resistant to the action of anaesthetic solutions’. This concept garnished a modicum of support, some proponents proposing that this effect might be due to reduced permeability of the roots. However, most were critical, suggesting such failures more likely reflect inactive solution, or a variety of anatomic variations or abnormalities such as arachnoid adhesions, unusual arrangements of the dentate ligament, or a dilated lower end of the thecal sac. Ultimately, the term ‘rachi-resistance’ disappeared from the anaesthesia literature.

A review article and two clinical studies in this issue of the British Journal of Anaesthesia attempt to shed light on this elusive subject. In their systematic review, Fettes and colleagues dissect the spinal technique into its sequential components, providing a framework to understand the mechanisms that may account for failure. Such information is a prerequisite for maximizing success rate, and for rational clinical management of a failed block. In the first of two related research papers, Ruppen and colleagues explore the cerebrospinal fluid (CSF) concentrations of anaesthetic associated with the development of adequate spinal anaesthesia after administration of plain bupivacaine 0.5%. Their principal finding was the enormous range of concentrations (26–781 μg ml⁻¹), which did not correlate with the level of block. Further, the variability in samples obtained at randomized time-points between 5 and 45 min post-injection was so large as to prohibit any meaningful pharmacokinetic assessment. An even larger variability (3.36–1020 μg ml⁻¹) was seen in the second study where samples were obtained from patients who had received the same anaesthetic but had inadequate anaesthesia. The range of concentrations from these two studies overlapped, with only four of the 20 failed spinals having a CSF concentration below any associated with successful spinal anaesthesia.

Although these findings may appear incomprehensible, they can be understood by appreciating the limitations of single-site assessments of CSF anaesthetic concentrations, a point well appreciated and considered by the authors of these two research papers. Because local anaesthetic will often distribute unevenly within the subarachnoid space, the concentration at a single point cannot be used to determine the true volume of distribution, nor can concentrations found below the conus reliably predict those at more rostral locations servicing clinically relevant dermatomes. Consequently, faced with a relatively low concentration, clinical correlation or imaging is needed to permit any distinction between a poor injection, a large volume of CSF below the conus, extensive spread, or an anomalous sample. With the exception of technical failure, similar considerations apply to interpretation of high concentrations.
Despite these limitations, there are some interesting insights that can be gleaned from the data. For example, the highest concentration in any sample came from a patient with inadequate anaesthesia, supporting the concept of maldistribution as an aetiology of failure, a point highlighted by the authors. A similar observation was made in a very early study of hyperbaric lidocaine administered through continuous spinal catheters. Of 16 patients receiving an initial injection of lidocaine 150–200 mg, there was only one failure requiring general anaesthesia. The anaesthetic concentration in the CSF sample from this patient was roughly 2 SD above the mean, and an X-ray demonstrated the catheter to be curled with the end resting in the cul-de-sac at the level of the second sacral vertebra. Such findings are also consistent with data obtained from in vitro investigations modelling subarachnoid anaesthetic distribution. That failure from maldistribution cannot be readily distinguished clinically from technical failure has important implications for management of a failed spinal. In such cases, repetitive injection can distribute in the same pattern, reinforcing the already high concentrations, and potentially resulting in neurotoxic injury. Review of the closed claims database and case reports appear to confirm these concerns. On the basis of these considerations, we previously made suggestions for management of a failed spinal, which included evaluation of the likelihood of technical error and adjustment of dosage for the second injection. However, these recommendations impart significant delay, as one must allow sufficient time for achievement of near-maximal block before assessment of sensory anaesthesia. A more efficient—and probably much safer—alternative is to simply limit the combined anaesthetic dosage to the maximum reasonable to administer as a single intrathecal injection.

In four of the failed spinals, there was no detectable sensory anaesthesia, despite CSF concentrations that exceeded the lowest value associated with a completely successful block. And, in one case, the concentration was above the 5th percentile for successful spinal anaesthesia, the cut-off (albeit somewhat arbitrary) that the authors thought should be adequate for successful spinal anaesthesia. Although it is possible that this reflects the limitations of sampling and errant concentrations obtained in the study of successful spinals, it is intriguing to consider the possibility that these patients were actually resistant to the anaesthetic. Such consideration is more than a theoretical possibility, as there are well-described mutations of the voltage-gated sodium channel that can profoundly affect function, including altered sensitivity to anaesthetic. Further advances in pharmacogenetics might thus identify genetic diversity as a factor in spinal anaesthetic failure, justifying a reintroduction of the term ‘rachi-resistance’ into the language of anaesthesia. Who knows, Sebrechts belief that there are familial tendencies in susceptibility, and that the ‘the Anglo-Saxon... has resistance to larger doses than the Italian’ might just turn out to be correct.

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FOCUS ON: REGIONAL ANAESTHESIA

Role of ultrasound in modern day regional anaesthesia

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Summary
The aim of any regional anaesthesia technique is to locate target nerves and deposit local anaesthetic around them. Nerve stimulation using anatomical landmarks has been conventional method of nerve localisation. With the advance in technology, the use of ultrasound in regional anaesthesia has been steadily increasing. In addition to localisation of nerves and other structures under direct visualisation, ultrasound has the potential to reduce complications and minimise the local anaesthetic toxicity by injecting right dose at the right site. The principles, advantages, disadvantages and applications of ultrasound have been reviewed in this article.

1. Introduction
Nerve blocks have been traditionally done using anatomical landmarks to guess approximate position of the nerve and then using either paraesthesia or nerve stimulation to confirm the proximity of needle to the nerve. This assumes that every person’s anatomy is same, yet we know that this assumption is wrong. There are interpersonal variations and also variations in the same person on different sides of the body. It is also assumed with these ‘blind techniques’ that when local anaesthetic is injected it spreads uniformly around the nerves which if does not happen results in block failure. Threshold current i.e. the current which indicates that the position of the stimulating needle is close to the nerve, but not close enough to cause nerve damage, is relatively poorly identified. It is possible to be actually eliciting paraesthesia or be intraneural with the needle without producing any motor response. Thus the science of nerve stimulation is neither precise nor perfect.

La Grange and his colleagues first reported the use of ultrasound for providing nerve block in 1978. They successfully performed supraclavicular brachial plexus blocks with the help of a Doppler ultrasound blood-flow detector to identify the subclavial artery.

2. Principles
Sound that we hear is between the frequency range of 20 and 20,000 Hz (20–20,000 cycles/s). An ultrasound probe (transducer) emits and receives high-frequency sound waves (greater than 20,000 cycles/s, 20 kHz) and thus ultrasound waves are not audible to the human ear. Ultrasound frequencies useful in clinical medicine are in the megahertz (MHz) range.

The ultrasound probe is a transducer that contains crystals which exhibit piezoelectric effect. Piezoelectricity is the ability of a substance to convert mechanical energy into electricity and vice versa. When an electrical current is applied to piezoelectric crystals (quartz) within the ultrasound probe, they vibrate resulting in ultrasound waves. As the ultrasound waves pass through body tissues of different acoustic impedance, the signals are attenuated. The degree of attenuation of signals depends on the attenuation coefficient of the tissue. Also, it varies directly with the frequency of the ultrasound wave and the distance from the source. Reflected waves are transformed into electrical signals by the transducer which are processed to generate an image on the screen.

Echogenicity or how bright the object appears depends on the amount of ultrasound reflected back to the probe; the greater the reflection, the brighter is the image and vice versa. Structures with high water content like blood let the ultrasound waves pass through with minimal reflection and so appear black or dark (hypoechoic). On the other hand, waves are reflected and scattered by the bone and tendons, hence these appear white or bright (hyperechoic). With bone, the periosteum appears as a white hyperechoic line. Structures of intermediate density such as the liver parenchyma or the thyroid gland reflect less. Hence they appear grey on the screen.

The depth of the structure from the probe is calculated by the software accounting for the speed of sound in tissue (1540 m/s on average) and the time taken for the ultrasound to return.

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3. Equipment

For anaesthesia purposes we need an ultrasound machine which is ideally small in size, portable as it is likely to be used between different theatres and different anaesthetists and durable as it has to move between theatres and by different anaesthetists so damage during transit is likely.

Colour Doppler is used to differentiate vascular from nonvascular structures. Low frequency probes (3–5 MHz) are useful to scan deeper structures like liver, gallbladder and kidneys while a frequency of 4–7 MHz is better for deep structures, such as the brachial plexus in the infracavicular region and the sciatic nerve in adults.

Superficial structures such as the supravcicular brachial plexus require high-frequency probes (10–16 MHz) that provide high axial resolution.

The hard disk should be high capacity with a CD burner in order to store and edit a large number of images and films although images and video can be stored on external hard disks as well.

As the competition between manufacturers is increasing and as the technology improves the machines are getting cheaper while the image quality is improving. Ultrasound machines used by the radiologists have multiple probes and softwares. They are useful for both diagnostic and therapeutic purposes. These are highly sophisticated, bulky and expensive varying from £100,000 to £150,000. Whereas a simple portable ultrasound machine for regional anaesthesia, peripheral arterial and central venous cannulation costs about £15,000.

4. Appearance of peripheral nerve under ultrasound

A single nerve fibre is surrounded by endoneurium. Group of nerve fibres forms a nerve fascicle. Each nerve fascicle is surrounded by perineurium. Nerve fascicles together form a nerve which is surrounded by epineurium. Nerve fibres themselves do not reflect any ultrasound so they appear dark. Only the connective tissue surrounding the nerve fibres, fascicles and the nerve itself reflects ultrasound and then appears bright or white.

On transverse (short-axis, nerve in cross-section) view that is generally used, a nerve is round or oval shaped with internal hypoechoic (dark) nerve fibres and nerve fascicles surrounded by connective tissue respectively.

In the long-axis view, the probe is parallel to the long axis of the nerve. In this view nerves appear tubular with parallel bright and dark bands corresponding to the fascicles and interfascicular connective tissue respectively.

Roots of the brachial plexus appear hypoechoic in the interscalene and supravcicular regions more like blood vessels without any flow. One possible explanation that has been suggested is that the nerves at this level have not grouped into fascicles yet. When the brachial plexus is scanned distally typical appearance of the peripheral nerve is seen.

Nerves vary in shape (round, oval or triangular) and a same nerve can have different shapes as it passes along different structures.

Nerves are fairly mobile structures as demonstrated by movement of the branches of the sciatic nerve in the popliteal fossa with foot movement. In order to identify the nerve anatomy it is terms of its size, depth and location before the insertion of needle, a preliminary scan should be performed. This helps in the assessment of point, angle and direction of needle insertion.

5. Advantages of ultrasound guided nerve identification

- Nerves can be easily identified. The structures surrounding the nerve like blood vessels (e.g. saphenous vein) can be easily identified which in turn can help the identification of the nerves.
- Needles can be visualised as a hyperechoic line. In real-time navigation of ultrasound, the needle can be guided towards the nerve. This can prevent the risk of inadvertent needle entry into the blood vessels, pleura or structures like spinal canal.
- Local anaesthetic spread can be seen with the ultrasound so if inadequate a further injection could be made. Incomplete nerve blocks can be prevented by ensuring circumferential spread of the local anaesthetic.
- Ultrasound can identify the point of division of the nerve. This is of help when complete nerve block before the division of nerve is needed as local anaesthetic can be injected proximal to the point of division of nerve identified by ultrasound.
- Placement of peripheral nerve catheters under direct vision.
- Ultrasound guided nerve blocks can be a relatively painless procedure when muscle contraction is avoided without nerve stimulation.
- In blocks such as the 3-in-1 block, it has been demonstrated that the success rate is higher using ultrasound and that the dose of local anaesthetic required is lower.
- Faster sensory onset time and longer duration of blocks.
- Improved quality of block.
- Less incidence of diaphragmatic paralysis as less volume can be used for interscalene block.
- No risk of radiation.

Patient groups where ultrasound guided blocks are particularly useful in:

- Children, in whom nerve blocks are performed under anaesthesia.
- Patients with peripheral neuropathy where it is difficult to elicit nerve stimulus although nerve damage can occur even without direct nerve needle contact.
- Use of Doppler has been described in obese patients or where the vascular landmarks can't be easily identified.

Ultrasound-assisted nerve block has been described for:

- Upper limb blocks: brachial plexus block by interscalene, supraclavicular, infracavicular and axillary approaches.
- Lower limb blocks: femoral nerve, lumbar plexus, sciatic nerve.
- Other nerve blocks: coeliac plexus, stellate ganglion, pudendal nerve.
- Assessment of the depth of the epidural space and to assess the lumbar epidural space during pregnancy.

Disadvantages of ultrasound guided nerve blocks:

- It has the potential to avoid or reduce nerve damage. Whether it can eliminate damage completely remains to be seen. Patient related factors and operator errors can still result in nerve damage.
- The ultrasound machines are still expensive although the cost is coming down.
6. Summary

Ultrasound has revolutionised the practise of regional anaesthesia. It has helped in a better understanding of the anatomic variability between patients. It has potential to provide a safe and reliable nerve block. It remains to be seen how it delivers this promise.

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