Extending epidural analgesia for emergency Caesarean section: a meta-analysis

S. G. Hillyard¹,²*, T. E. Bate², T. B. Corcoran¹,³, M. J. Paech³,⁴ and G. O'Sullivan²

¹ Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Wellington Street Campus, Box X2213 GPO, Perth, WA 6847, Australia
² Department of Anaesthesia, Guy’s and St Thomas’ NHS Foundation Trust, London SE1 7EH, UK
³ School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia
⁴ Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, Perth, WA, Australia

* Corresponding author. E-mail: sghillaryard@yahoo.co.uk

Summary. There is no high-level evidence supporting an optimal top-up solution to convert labour epidural analgesia to surgical anaesthesia for Caesarean section. The aim of this meta-analysis was to identify the best epidural solutions for emergency Caesarean section anaesthesia, with respect to rapid onset and low supplementation of intraoperative block. Eleven randomized controlled trials, involving 779 parturients, were identified for inclusion after a systematic literature search and risk of bias assessment. ‘Top-up’ boluses were classified into three groups: 0.5% bupivacaine or levobupivacaine (Bup/Levo); lidocaine and epinephrine, with or without fentanyl (LE ± F); and 0.75% ropivacaine (Ropi). Pooled analysis using the fixed-effects method was used to calculate the mean difference (MD) for continuous outcomes and risk ratio (RR) for dichotomous outcomes. Lidocaine and epinephrine, with or without fentanyl, resulted in a significantly faster onset of sensory block [MD −4.51 min, 95% confidence interval (CI) −5.89 to −3.13 min, P<0.00001]. Bup/Levo was associated with a significantly increased risk of intraoperative supplementation compared with the other groups (RR 2.03; 95% CI 1.22–3.39; P = 0.007), especially compared with Ropi (RR 3.24, 95% CI 1.26–8.33, P = 0.01). Adding fentanyl to a local anaesthetic resulted in a significantly faster onset but did not affect the need for intraoperative supplementation. Bupivacaine or levobupivacaine 0.5% was the least effective solution. If the speed of onset is important, then a lidocaine and epinephrine solution, with or without fentanyl, appears optimal. If the quality of epidural block is paramount, then 0.75% ropivacaine is suggested.

Keywords: Caesarean section; epidural anaesthesia; epidural analgesia

Converting labour epidural analgesia to surgical anaesthesia for Caesarean section is a common procedure. Over 93 000 emergency Caesarean sections (EmCS) were carried out in NHS hospitals in England from 2008 to 2009, and in 22% of these, an epidural anaesthetic was used.¹ This is consistent with the findings of a large-scale audit that noted that an epidural bolus (‘top-up’) was the mode of anaesthesia in 26% of EmCS.² Although many women are managed this way, the best way to convert epidural analgesia to anaesthesia for EmCS remains unclear. Opinion remains divided, with a recent survey indicating that a wide range of local anaesthetic (LA) solutions are used to achieve epidural anaesthesia.³ There have been several randomized controlled trials examining the efficacy of different LAs and adjuncts, but none has clarified the optimal solution. The primary focus of these studies was to establish which epidural solution achieves anaesthesia in the fastest time. A lidocaine and epinephrine combination appears to result in a rapid onset of anaesthesia.⁴–⁷ However, another important characteristic of the solution is that it should be fully effective for the duration of surgery, thereby minimizing intraoperative breakthrough pain, an important medico-legal issue in obstetric anaesthesia. This outcome has often been a secondary endpoint in studies of anaesthesia for EmCS, so trials often have insufficient power to adequately assess this endpoint. Inadequate study power may also occur because of the unpredictable nature of EmCS, such that recruitment and data collection are difficult. Several trials were halted before the planned number of patients had been recruited.⁶ ⁸ ⁹

The aim of this meta-analysis was to identify whether the current evidence supported significant differences between the various epidural ‘top-up’ solutions with respect to the time to the onset of surgical anaesthesia and the incidence of intraoperative supplementation.

Methods

We identified studies that evaluated conversion of epidural analgesia during labour to surgical anaesthesia for EmCS (Fig. 1). This involved searching Google Scholar, MEDLINE...
(1950 to 2010), EMBASE (1974 to 2010), CINAHL (1982 to 2010), and the Cochrane Library. For these database searches, we used the following exploded medical subject headings (MeSH), text words, and Boolean operators: ‘epidural’ OR ‘extradural’ AND ‘cesarean section’ OR ‘cesarean delivery’ AND ‘urgent’ OR ‘emergency’. The search was not limited to publications in the English language and was last conducted on September 14, 2010. The authors then examined available abstracts from the 2000–2010 meetings of The American Society of Anesthesiologists, The American Society of Regional Anesthesia and Pain Medicine, The European Society of Anaesthesia, The European Society of Regional Anaesthesia and Pain Therapy, The International Anesthesia Research Society, and the Society for Obstetric Anaesthesia and Perinatology. Abstracts from the 1991–2010 meetings of the Obstetric Anaesthetist’s Association were also reviewed. The reference lists of all the relevant articles generated by the above searches were then hand-searched for further studies.

Duplicates were removed and the remaining references analysed independently by two investigators to determine whether they met the inclusion criteria. Studies were considered eligible if they were randomized controlled trials comparing differing epidural top-up solutions, to extend labour analgesia achieved using a low-dose mixture of LA and opioid, for an EmCS.

Data from the trials included were extracted individually by two of the authors (S.G.H. and T.E.B.) on to a predetermined spreadsheet, with any discrepancies resolved by re-examining the original article or consulting a third author (T.B.C.). The authors of the selected trials were contacted to determine whether supplementary or unpublished data were available. The primary outcome measures were time to onset of a block adequate for surgery and the need

Fig 1 Search strategy flowchart.
for supplementation of the block intraoperatively. Secondary outcomes included: nausea and vomiting, pruritus, shivering, sedation, cardiovascular changes, motor block, maternal satisfaction scores, Apgar scores, and cord gases. Details of labour analgesia, methods of the epidural top-up, block assessment, and the duration of surgery were also recorded. Information on sequence generation, allocation concealment, blinding, outcome details, and other potential sources of bias were noted, to allow implementation of The Cochrane Collaboration’s tool for assessing the risk of bias.10

The individual trials evaluated a variety of epidural top-up solutions made up of differing LAs and adjuncts. For analysis, the epidural solutions were classified into three groups based on the LA that each contained: 0.5% bupivacaine or levobupivacaine (group Bup/Levo); 0.2% lidocaine with 1:200 000 epinephrine, with or without fentanyl (group LE±F), and 0.75% ropivacaine (group Ropi).

Continuous outcomes were most often reported as median, inter-quartile range (IQR), and range. We calculated the mean and standard deviation via a validated technique before meta-analysis.11 Descriptive statistics were then used to calculate the mean difference (MD), using the fixed-effects inverse variance approach. Results are expressed as MD with 95% confidence interval (CI) and results considered significant if the P-value was <0.05. For dichotomous outcomes, a meta-analysis was performed using risk ratio (RR) and the Mantel–Haenszel fixed-effects method.12 13 Results are given as RR, with 95% CI. A P-value of <0.05 was considered significant.

The degree of heterogeneity was measured and expressed as the χ²-statistic. Inconsistency was assessed using the I²-statistic,14 15 with a value of >40% indicative of significant heterogeneity.

Sensitivity analysis based on the outcomes of onset of block and intraoperative supplementation was performed by excluding trials that did not have double blinding, adequate allocation concealment, or a loss to follow-up of >10%. A funnel plot of each primary outcome was used to assess publication bias. All statistical analysis was conducted using Review Manager version 5.0.25 for Windows.16

Results

A total of 11 randomized controlled trials involving 779 parturients met the criteria for inclusion4–9 17–21 (Table 1). The trials were predominantly conducted in the UK,4–9 19 21 with three from Asia,17 18 20 and all published in English. Two of the trials were presented only as conference abstracts,19 21 and further trial details were obtained directly from the authors. Overall, the trials were of high quality (risk of bias summary, Fig. 2).

All trials recruited labouring women who had epidural catheters in situ and were receiving a low-dose mixture of LA and fentanyl, administered by various methods.

Inclusion and exclusion criteria were similar among the individual trials. All but one trial18 were limited to singleton pregnancies, four were restricted to nulliparous women,4–9 17 and the rest recruited women of any parity.4–6 18–21 One trial was limited to category 3 EmCS17 and four to category 2 and 3 EmCS,5 6 18 20 while the others included all categories of EmCS.4 7–9 19 21

Onset of surgical block

In many studies, the onset of surgical block was assessed using more than one modality of block assessment or sought different dermatomal levels before surgery was allowed to proceed (Table 2). Most of the studies used loss of ‘cold’ to T4,4 7–9 17–19–21 but two measured ‘touch’ to T5.5 9 and two ‘touch’ to T7.5 6 Loss of ‘sharp’ sensation was also assessed in three trials, but at different levels, namely T4,17 T6,18 and T76 (Table 2).

Analysis indicated a significant reduction in the time to the onset of block when LE±F solutions were compared with either Bup/Levo or Ropi (overall MD −1.66 min, 95% CI −2.40 to −0.91 min, P<0.0001; Fig. 3). There was, however, considerable heterogeneity among the trials (P<0.0001 and I²=83%) which appeared to be accounted for mainly by one trial.20 Removal of this trial from the meta-analysis, due to its markedly different protocol, reduced the time to the onset of block after LE±F solutions further (MD −4.51 min, 95% CI −5.89 to −3.13 min, P≤0.00001), with a concurrent decrease in the degree of heterogeneity (P=0.74 and I²=0%). Adding 50–75 μg of fentanyl to a top-up solution decreased the onset time to surgical anaesthesia (overall MD −2.02 min, 95% CI −3.31 to −0.73 min, P=0.002). The two trials in this meta-analysis showed low heterogeneity (P=0.29 and I²=11%; Fig. 4).

Intraoperative block supplementation

Meta-analysis showed a significant increase in the incidence of supplementation for intraoperative pain when Bup/Levo was compared with either LE±F or Ropi (pooled RR 2.03, 95% CI 1.22–3.39, P=0.007; Fig. 5). There was no heterogeneity among these trials (P=0.73 and I²=0%). This increased risk of intraoperative supplementation was highest in the pooled subgroup analysis of Bup/Levo compared with Ropi (RR 3.24, 95% CI 1.26–8.33, P=0.01). Again there was no heterogeneity (P=0.57 and I²=0%). When Bup/Levo was compared with LE±F, the results were not significant (RR 1.60, 95% CI 0.86–2.98, P=0.13), with no evidence of heterogeneity (P=0.80 and I²=0%). Removal of the only unpublished study included in the meta-analysis of intraoperative supplementation21 resulted in a marginal reduction in the relative risk of intraoperative supplementation associated with Bup/Levo (RR 1.95, 95% CI 1.15–3.30, P=0.01), with no implications for heterogeneity (P=0.66 and I²=0%).

The addition of fentanyl to an epidural top-up did not decrease the need for intraoperative supplementation (pooled values RR 0.66, 95% CI 0.33–1.33, P=0.25), although there was heterogeneity among these trials (P=0.01 and I²=85%; Fig. 6).
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Top-up solution A (volume in ml)</th>
<th>Top-up solution B (volume in ml)</th>
<th>Top-up solution C (volume in ml)</th>
<th>Details of labour analgesia</th>
<th>Administration details of epidural top-up</th>
<th>Primary outcome/s</th>
<th>Median pre-top-up level of blockade A/B/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders and colleagues⁴</td>
<td>47</td>
<td>0.5% bupivacaine (20)</td>
<td></td>
<td>0.75% ropivacaine (20)</td>
<td>Midwife top-up: 10 ml of 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T10/T10 (cold)</td>
</tr>
<tr>
<td>Hillyard and colleagues²⁷</td>
<td>61</td>
<td>0.5% levobupivacaine (15)</td>
<td></td>
<td>0.75% ropivacaine (15)</td>
<td>PCEA: 9.9 ml (20 min lockout) 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T9/T9 (cold)</td>
</tr>
<tr>
<td>Sng and colleagues⁸</td>
<td>90</td>
<td>0.5% levobupivacaine (15)</td>
<td>2% lidocaine, epinephrine 1:200 000 and 50 μg fentanyl (15)</td>
<td>0.75% ropivacaine (15)</td>
<td>GSE : 2 mg ropivacaine+15 μg fentanyl IT, then infusion: 0.1% ropivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T9/T8/T9 (cold)</td>
</tr>
<tr>
<td>Bolaji and colleagues⁶</td>
<td>100</td>
<td>0.5% levobupivacaine (20)</td>
<td>2% lidocaine, epinephrine 1:200 000 and 100 μg fentanyl (22.1)</td>
<td></td>
<td>Intermittent top-up: 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>3 ml test dose over 90–120 s, the rest over 1–2 min</td>
<td>Time from end of top-up until onset of block to touch at T7</td>
<td>T11/T11 (sharp)</td>
</tr>
<tr>
<td>Goring-Morris and Russell³</td>
<td>68</td>
<td>0.5% bupivacaine (20)</td>
<td>2% lidocaine, epinephrine 1:200 000 and 100 μg fentanyl (22.1)</td>
<td>50:50, 0.5% bupivacaine and 2% lidocaine and epinephrine 1:200 000 (20)</td>
<td>Midwife top-up: 10 ml of 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl (max every 30 min)</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until block to cold at T4</td>
<td>T10/T10/T10 (cold)</td>
</tr>
<tr>
<td>Lucas and colleagues⁷</td>
<td>90</td>
<td>0.5% bupivacaine (20)</td>
<td>2% lidocaine and epinephrine 1:200 000 (20)</td>
<td></td>
<td>PCEA: 5 ml (15 min lockout)+3 ml background. 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T10/T8 (cold)</td>
</tr>
<tr>
<td>Alam and colleagues⁹</td>
<td>46</td>
<td>0.5% levobupivacaine (20)</td>
<td>1.8% lidocaine, epinephrine 1:200 000 and HCO₃⁻ (20.1)</td>
<td></td>
<td>Infusion: 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>3 ml test dose over 3 min, the rest over 1 min</td>
<td>Time from end of top-up until loss of sharp discrimination at T6</td>
<td>T11/T11 (sharp)</td>
</tr>
<tr>
<td>Lam and colleagues¹⁸</td>
<td>40</td>
<td>2% lidocaine, epinephrine 1:200 000 75 μg fentanyl and HCO₃⁻ (16.2)</td>
<td>2% lidocaine, epinephrine 1:200 000 and 75 μg fentanyl (16.2)</td>
<td></td>
<td></td>
<td></td>
<td>Time from end of top-up until block to cold at T4</td>
<td>T12/L1 (cold)</td>
</tr>
<tr>
<td>Hong and colleagues¹⁷</td>
<td>62</td>
<td>2% lidocaine, epinephrine 1:200 000 and 100 μg fentanyl (22)</td>
<td>2% lidocaine and epinephrine 1:200 000 (22)</td>
<td></td>
<td>Infusion: 0.1% ropivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 5 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T12/L1 (cold)</td>
</tr>
<tr>
<td>Bolad and colleagues¹⁹</td>
<td>63</td>
<td>0.5% bupivacaine (15)</td>
<td>0.5% levobupivacaine (15)</td>
<td>0.75% levobupivacaine (15)</td>
<td>PCEA: 9.9 ml (20 min lockout) 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until onset of block to cold at T4</td>
<td>T9/TB (cold)</td>
</tr>
<tr>
<td>Malhotra and Yentis⁹</td>
<td>112</td>
<td>0.5% levobupivacaine and 75 μg fentanyl (21.5)</td>
<td>0.5% levobupivacaine (21.5)</td>
<td></td>
<td>Midwife top-up: 10–15 ml of 0.1% bupivacaine and 2 μg ml⁻¹ fentanyl (max every 30 min)</td>
<td>Total volume over 3 min</td>
<td>Time from end of top-up until block to cold at T4</td>
<td>T9/T8 (cold) T8/T10 (touch)</td>
</tr>
</tbody>
</table>
Secondary outcomes

Intraoperative nausea and vomiting was recorded either as the incidence of nausea, vomiting, or both, a nausea and vomiting score, or as the occurrence of nausea only. Most recorded the incidence of intraoperative vomiting. Pooled analysis of trials comparing an epidural top-up with or without fentanyl showed no difference in the rates of intraoperative vomiting and no heterogeneity (RR 0.81, 95% CI 0.53–1.25, P = 0.35, I^2 = 0%).

Cardiovascular outcomes measured in the studies included the lowest mean heart rate or systolic blood pressure, the need for vasopressors, the mean dose of vasopressors, and the mean volume of i.v. fluids administered. Six trials documented the incidence of hypotension, with none finding any differences between solutions. Hypotension was not reduced by the presence of epinephrine in the epidural top-up (RR 0.97, 95% CI 0.74–1.29, P = 0.85, I^2 = 0%).

Neonatal outcomes were reported in nine trials, and there were no differences in Apgar scores or umbilical artery blood gas measurements detailed in any of the individual studies.

Publication bias and sensitivity analysis

After restricting the analysis to studies that were both double-blinded and showed adequate allocation concealment, the onset time of a surgical block was slightly significantly shorter for LE + F compared with Bup/Levo or Ropi (MD −0.89 min, 95% CI −1.72 to −0.07 min, P = 0.03, I^2 = 71%). Identical sensitivity analysis for intraoperative supplementation changed the findings of an increased risk associated with Bup/Levo compared with LE ± F or Ropi to non-significant (RR 1.81, 95% CI 0.95–3.44, P = 0.06, I^2 = 0%). The subgroup analysis of Bup/Levo compared with Ropi was unchanged (RR 3.13, 95% CI 1.19–8.27, P = 0.02).

A funnel plot using the primary outcomes as endpoints did not indicate the presence of publication bias.

Discussion

This meta-analysis demonstrates that this is an area of obstetric anaesthesia practice that has not been comprehensively studied. Only 11 randomized controlled trials met the inclusion criteria that we considered to represent common practice in obstetric anaesthesia. Our findings suggest that a lidocaine 2% with epinephrine + fentanyl solution provides the fastest onset of surgical block, while ropivacaine 0.75% results in the lowest incidence of intraoperative supplementation. The addition of fentanyl to the top-up solution does not reduce the need for intraoperative supplementation but may decrease the onset time.

Owing to the variety of different epidural top-up solutions used in these trials, we classified the solutions based on their main LA component, to enable comparisons from the majority of the trials that met the inclusion criteria. We believe that combining levobupivacaine 0.5% and bupivacaine 0.5% into one group was justified, because these drugs have similar potency and similar clinical effect when administered epidurally for Caesarean section.
Table 2  Time to onset of block for each of the epidural top-up solutions, modality through which this was assessed and from which point after administration of the top-up this time commenced. Values are median [IQR (range)]

<table>
<thead>
<tr>
<th>Study</th>
<th>Top-up solution A</th>
<th>Top-up solution B</th>
<th>Top-up solution C</th>
<th>Assessment method 1</th>
<th>Time for A</th>
<th>Time for B</th>
<th>Time for C</th>
<th>Assessment method 2</th>
<th>Time for A</th>
<th>Time for B</th>
<th>Time for C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders and colleagues</td>
<td>0.5% Bup</td>
<td>0.75% Ropi</td>
<td>Cold T4 (end of top-up)</td>
<td>11 [7.3–19.5 (5.0–45.0)]</td>
<td>11 [8.5–15.5 (6.0–20.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hillyard and colleagues</td>
<td>0.5% Levo</td>
<td>0.75% Ropi</td>
<td>Cold T4 (end of top-up)</td>
<td>7.5 [5.0–15.0 (5.0–35.0)]</td>
<td>10 [7.5–15.0 (5.0–35.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sng and colleagues</td>
<td>0.5% Levo 2% Lido/Epi and 50 μg Fent</td>
<td>0.75% Ropi</td>
<td>Cold T4 (end of top-up)</td>
<td>10.0 [7.0–15.0 (5.0–20.0)]</td>
<td>9.5 [7.0–13.3 (5.0–19.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balaji and colleagues</td>
<td>0.5% Levo 2% Lido/Epi and 100 μg Fent</td>
<td>Touch T7 (end of top-up)</td>
<td>15 [10.0–20.0 (5.0–40.0)]</td>
<td>10 [8.0–13.0 (5.0–25.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goring-Morris and Russell</td>
<td>0.5% Bup 2% Lido/Epi and 100 μg Fent</td>
<td>Touch T7 (start of top-up)</td>
<td>17.5 [12.5–25.0 (7.5–40.0)]</td>
<td>13.8 [10.0–26.9 (2.5–32.5)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucas and colleagues</td>
<td>0.5% Bup 2% Lido/Epi</td>
<td>0.5% Bup and 2% Lido/Epi</td>
<td>Cold T4 (end of top-up)</td>
<td>14 [11.0–19.3 (6.0–25.0)]</td>
<td>10 [9.0–18.5 (6.0–36.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allam and colleagues</td>
<td>0.5% Levo 1.8% Lido/Epi and HCO3</td>
<td>2% Lido/Epi and 100 μg Fent</td>
<td>Cold T4 (end of top-up)</td>
<td>11 [9.0–14.0 (6.0–30.0)]</td>
<td>7 [5.0–8.0 (4.0–17.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lam and colleagues</td>
<td>2% Lido/Epi 100 μg Fent and HCO3</td>
<td>2% Lido/Epi and 100 μg Fent</td>
<td>Sharp T6 (end of top-up)</td>
<td>6 [4.0–6.0 (2.0–8.0)]</td>
<td>10 [8.0–10.0 (4.0–12.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong and colleagues</td>
<td>2% Lido/Epi 2% Lido/Epi and 100 μg Fent</td>
<td>Cold T4 (end of top-up)</td>
<td>15.0 [12.5–17.5 (7.5–20.0)]</td>
<td>12.5 [10.0–17.5 (5.0–17.5)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolad and colleagues</td>
<td>0.5% Levo 0.75% Levo</td>
<td>0.5% Bup</td>
<td>Cold T4 (end of top-up)</td>
<td>15 [5.0–30+]</td>
<td>15 [5.0–40.0]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malhotra and Yentis</td>
<td>0.5% Levo 0.5% Levo and 75 μg Fent</td>
<td>Cold T4 (end of top-up)</td>
<td>11 [7.0–16.0 (3.0–48.0)]</td>
<td>10 [5.0–14.0 (5.0–29.0)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The study of Bolad and colleagues includes a top-up solution of 0.5% Levo 0.75% Levo and 0.5% Bup. The study of Malhotra and Yentis includes a top-up solution of 0.5% Levo 0.5% Levo and 75 μg Fent.
other LAs in the meta-analysis of onset time, because they have been found consistently to have faster onset.4-7 25 26

Drawing conclusions from this meta-analysis is complicated by the diversity of protocols and endpoints, this being most apparent in the investigation of onset. In total, six different combinations of sensory block testing modality and level of block were recorded, adding complexity to interpretation of results. The implications for research generated by the lack of consensus relating to suitable block levels and methods of measurement have been highlighted before.27 The starting point for recording onset time also varied, with the majority of trials using the end of administration of the epidural top-up, but one the beginning6 and another including a 3 min test dose before using the end of the main epidural top-up.17 Such diversity may affect the validity of the meta-analytical techniques applied to this

Fig 3 The onset time of a block suitable to allow surgery, comparing LE ± F (2% lidocaine, epinephrine, and fentanyl) top-up solutions with either Bup/Levo (0.5% bupivacaine, 0.5% levobupivacaine), or Ropi (0.75% ropivacaine) solutions.

Fig 4 The effect of the addition of fentanyl to a top-up solution on the onset time of a block suitable to allow surgery.

Fig 5 The need for intraoperative supplementation, comparing Bup/Levo (0.5% bupivacaine or 0.5% levobupivacaine) top-up solutions to LE ± F (2% lidocaine, epinephrine, and Fentanyl), or Ropi (0.75% ropivacaine) solutions.
and endpoint. However, in each study, these different endpoints were all considered similarly to indicate surgical readiness, arguably assessing the same clinical endpoint and therefore making meta-analysis appropriate.

If the upper limit of the range of onset times is considered to be the longest expected time for an epidural top-up to achieve anaesthesia for surgical readiness, then all of the solutions studied could be considered appropriate for a category 3 EmCS,28 for which a suggested decision to delivery interval is <75 min.29 When there is maternal or fetal compromise, delivery should be accomplished as quickly as possible, taking into account that rapid delivery has the potential to do harm.28 A category 1 EmCS has an accepted audit standard of <30 min for the decision-to-delivery interval,28 so most of the top-up solutions would be suitable for most of these circumstances, as indicated by their IQR and range for onset time. Inevitably, there are possible exceptions, such that the reduction in onset time by 4.5 min after administration of lidocaine 2% and epinephrine, with or without fentanyl, appears attractive.

The recent ‘Saving Mothers Lives’ report emphasizes the importance of fast speed of block onset after an epidural top-up in certain situations.30 One of the deaths directly due to anaesthesia resulted from inability to ventilate the lungs during general anaesthesia for a Category 1 Caesarean section. This woman had a functioning epidural catheter in the delivery room, that location being recommended in the report providing an anaesthetist and suitable equipment is available, creates the opportunity for surgical readiness comparable with administering general anaesthesia, which has a higher risk of serious complications.

Although there were insufficient trials to assess the effect of bicarbonate in this meta-analysis, the reduction in onset time appears more pronounced when bicarbonate is added.4 18 Some of the time-saving might, however, be offset by drug preparation time,31 and there are safety implications when mixing drugs in an emergency situation.32 Despite an absence of case reports of clinical toxicity in this setting in which plasma and tissue LA concentrations have already been established by epidural analgesia, lidocaine is a less cardiotoxic LA than bupivacaine, levobupivacaine, or ropivacaine.

The need for intraoperative supplementation of the epidural block was recorded more consistently across studies. If either levobupivacaine 0.5% or bupivacaine 0.5% is used then supplementation is more likely to be needed, especially compared with ropivacaine 0.75%. The potency ratio of levobupivacaine and bupivacaine to ropivacaine ranges from approximately 1.2 to 1.1.33 34 At elective CS5 36 or for labour analgesia,57 38 potencies appear similar. It may be that preceding epidural analgesia causes a degree of tachyphylaxis to LA,39 such that a larger dose is required in the emergency setting. If ropivacaine, bupivacaine, and levobupivacaine have similar potencies, then the more concentrated solution of ropivacaine (0.75% vs 0.5%) may explain why it appears a more effective solution.

The potency ratio of lidocaine to bupivacaine is commonly reported to be 1:410 and the doses administered in the trials reflect this. The risk of intraoperative supplementation was not significantly different between Bup/Levo and LE ± F solutions. This may be due to the use of similarly effective doses or the presence of epinephrine, which reduces vascular uptake of lidocaine61 and prolongs its action.

Fentanyl is often added to an epidural top-up in this setting, but the meta-analysis did not support a benefit in reducing the need for supplementation of the block intraoperatively. A major limitation of the finding is that it was generated by pooling only two trials,9 16 which reported contradicting results. In contrast, the addition of fentanyl significantly improves the quality of epidural anaesthesia for elective surgery.62 It has been suggested that this difference observed in the emergency situation is because fentanyl in the labour epidural solution has already produced a near-maximal effect.9 The onset time was reduced by the inclusion of fentanyl and it did not increase the incidence of vomiting, so further investigation of its effect on the quality of block appears warranted.

A potentially confounding factor in this meta-analysis was the inclusion of the study by Sng and colleagues20 that had different methodology to the other trials. In that trial, labour epidural analgesia was initiated with a combined spinal–epidural technique and any epidural top-up that did
not produce a rapid effect was quickly topped up further before operation. This approach might account for the absence of a difference in onset time or intraoperative supplementation rate between the study solutions. When this study was excluded, lidocaine with epinephrine, with or without fentanyl, showed a greater, and clinically relevant, reduction in onset time compared with other solutions.

The merit of including unpublished studies in a meta-analysis can be questioned. Two unpublished trials met the inclusion criteria, one of which was used in the meta-analysis of intraoperative supplementation. The majority of investigators involved in meta-analyses feel that unpublished studies should be included, with the caveat that it has been possible to assess their methodology adequately. We were able to answer adequately the same risk of bias questions asked of the published trials and therefore were willing to include them. To investigate the effects of including unpublished material, we removed the one unpublished trial from the meta-analysis of intraoperative supplementation. This led to small reduction in the increased risk of supplementation associated with Bup/Levo, but the MD from other groups remained significant.

Another possible criticism of this meta-analysis is the absence of trials evaluating 3% 2-chloroprocaine, which is widely used as an epidural top-up solution for EmCS in North America. This LA has a rapid onset, but a short duration of action, and is not available in the UK. The two trials assessing its efficacy in these circumstances did not meet the inclusion criteria for this analysis.

In conclusion, the current literature does not strongly support one particular epidural top-up solution when converting labour epidural analgesia to epidural anaesthesia for surgery. Meta-analysis of the few trials investigating this topic was limited by both small numbers of trials and methodological variance, but indicates that bupivacaine or levobupivacaine 0.5% is the least efficacious with respect to both the speed of onset and quality of block. Ropivacaine 0.75% is most effective for reducing the need for supplementation of intraoperative block, while lidocaine 2% with epinephrine, with or without fentanyl, produces the fastest onset of surgical block.

This meta-analysis highlights the need for a multicentre, double-blinded, randomized controlled trial to address the question of the optimal solution for EmCS. Such a trial would need to be powered adequately for the incidence of intraoperative supplementation and onset time of block and should use a method of block assessment that is widely supported and clinically applicable. Until further information is available, if a rapid onset block is required, such as for a category 1 EmCS, using lidocaine 2% with epinephrine, and probably fentanyl, is recommended. Clinical trials also suggest that adding bicarbonate is beneficial in these circumstances, but there were insufficient such trials to perform meta-analysis and drug preparation time must be considered. When there is less time pressure, ropivacaine 0.75% appears optimal because it is associated with a reduced need for intraoperative supplementation.

Acknowledgement

We would like to thank Prof. F. Reynolds for her appraisal and helpful criticism of the paper.

Conflict of interest

None declared.

Funding

We received no funding for this meta-analysis.

References


18 Lam DT, Ngaan Kee WD, Khaw KS. Extension of epidural blockade in labour for emergency Caesarean section using 2% lidocaine with epinephrine and fentanyl, with or without alkalinisation. Anaesthesia 2001; 56: 790–4


20 Sng BL, Pay LL, Sia ATH. Comparison of 2% lignocaine with adrenaline and fentanyl, 0.75% ropivacaine and 0.5% levobupivacaine for extension of epidural analgesia for urgent caesarean section after low dose epidural infusion during labour. Anaesth Intensive Care 2008; 36: 659–64


24 Bader AM, Tsen LC, Camann WR. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. Anesthesiology 1999; 90: 1596–601


26 Norton AC, Davis AG, Spicer RJ. Lignocaine 2% with adrenaline for epidural Caesarean section: a comparison with 0.5% bupivacaine. Int J Obstet Anaesth 1999; 8: 425–30


33 Brau ME, Branitzki P, Olschewski A. Block of neuronal tetrodotoxin-resistant Na⁺ currents by stereoisomers of piperidine local anesthetics. Anesth Analg 2000; 91: 1499–505


35 Crosby E, Sandler A, Finucane B, et al. Comparison of epidural anaesthesia with ropivacaine 0.5% and bupivacaine 0.5% for caesarean section. Can J Anaesth 1998; 45: 1066–71


38 Benhamou D, Ghosh C, Mercier FJ. A randomized sequential allocation study to determine the minimum effective analgesic concentration of levobupivacaine and ropivacaine in patients receiving epidural analgesia for labour. Anesthesiology 2003; 99: 1383–6


45 Laishley RS, Morgan BM, Reynolds F. Effect of adrenaline on extradural anaesthesia and plasma bupivacaine concentrations during caesarean section. Br J Anaesth 1988; 60: 180–6


54 Dickson MAS, Jenkins J. Extension of epidural blockade for emergency Caesarean section. Assessment of a bolus dose of bupivacaine 0.5% 10 ml following an infusion of 0.1% for analgesia in labour. *Anaesthesia* 1994; 49: 636–8