Effect of epidural volume extension on dose requirement of intrathecal hyperbaric bupivacaine at Caesarean section

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Background. The technique of epidural volume extension (EVE) involves the injection of saline into the extradural space immediately following the intrathecal injection, as part of a combined spinal-epidural (CSE) anaesthetic. One of the suggested benefits of EVE is a reduction in local anaesthetic required. The aim of this study was to test this hypothesis by comparing the median effective doses (ED50) of hyperbaric bupivacaine with fentanyl 25 \( \mu g \) with and without EVE for Caesarean section.

Methods. Sixty women were randomized to receive either CSE anaesthesia with EVE (EVE group) or no EVE (NEVE group). Using a double-blinded, up-down sequential technique, varying doses of bupivacaine with fentanyl 25 \( \mu g \) were administered. ED50 was estimated from up-down reversals and probit regression.

Results. The ED50 for bupivacaine was similar and not significantly different in the two groups (5.1 mg in the EVE and 6.1 mg in the NEVE group; difference 1.0 mg, 95% CI –0.12 to 2.2, \( P = 0.08 \)).

Conclusions. This study illustrates that whilst low doses of intrathecal bupivacaine can be effectively used for Caesarean section, at such doses EVE does not appear to offer reliable or clinically relevant reductions in dosing with intrathecal bupivacaine.


Keywords: anaesthetic techniques, epidural volume extension; anaesthetics local, intrathecal bupivacaine

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The technique of injecting normal saline into the extradural space following an intrathecal injection is known as epidural volume extension (EVE) and has been shown to increase the cephalad spread of the block.\(^1\)\(^2\) It is not known whether this represents a true dose sparing effect, allowing smaller doses of local anaesthetic to be used to similar effect. The aim of this study was to determine whether or not EVE did have a dose sparing effect on bupivacaine requirements for Caesarean section by comparing the median effective dose (ED50) of intrathecal bupivacaine with 25 \( \mu g \) fentanyl, with and without EVE.

Methods

Having been granted ethics committee approval, written informed consent was obtained from parturients who were ASA Physical Status I or II, more than 37 weeks of gestation, with a singleton uncomplicated pregnancy, booked to deliver by elective Caesarean section, with combined spinal-epidural (CSE) anaesthesia. Parturients weighing more than 100 kg, or with pre-eclampsia, pregnancy-induced hypertension, in active labour or presenting for emergency Caesarean section were excluded. The study design was prospective, double-blinded sequential allocation.

All participants received Hartmann’s solution 500 ml i.v. as a preload, and baseline arterial pressure was determined by calculating the mean of three preoperative readings taken in theatre immediately before induction. The skin was infiltrated with lidocaine 1%w/v and a 16G Tuohy needle used to identify the epidural space with loss of resistance to saline at the L2–3 or L3–4 interspace with the parturient in the left lateral position. A 27G Whitacre spinal needle was then passed via the Tuohy needle to puncture the dura with the orifice pointing cephalad. The study solution was injected over 15–20 s and CSF was aspirated before and after injection to confirm intrathecal placement. The spinal needle was removed, and depending on group allocation, the parturient either received EVE via the epidural needle with subsequent placement of the epidural catheter, or the epidural catheter was immediately threaded into the space. Having secured the catheter, parturients were turned into the right lateral position within 3 min of spinal injection. As is our routine,
oxygen 4 litre min\(^{-1}\) was administered via face mask and continuous cardiotocograph monitoring was instituted 10 min before intrathecal injection and continued until the start of surgery. Non-invasive arterial pressure was recorded every minute up until delivery and subsequently at 5-min intervals in accordance with local protocol. Hypotension was defined as a systolic arterial pressure (SAP) of less than 100 mm Hg, a decrease of more than 20% from baseline SBP, or onset of nausea and was treated with ephedrine 6 mg boluses.

Subjects were randomized in pairs using sealed opaque envelopes into two groups to receive CSE with saline 0.9% w/v 7 ml through the epidural needle injected over 10 s (EVE group) or without EVE (NEVE group). An up-down sequential allocation technique was used to allocate bupivacaine dose to each parturient with the first patient in each group receiving 10 mg hyperbaric bupivacaine at room temperature with 25 µg fentanyl, a dose arbitrarily chosen. Anaesthesia was assessed using touch, as opposed to cold, to ethyl chloride spray bilaterally. An effective dose was defined as one that resulted in a sensory block to the xiphisternum within 20 min of the intrathecal injection, with no requirement for an extradural top-up within 45 min. The dosing interval was 1 mg hyperbaric bupivacaine and the dose of fentanyl remained constant throughout the study. An ineffective intrathecal dose was topped up via the epidural catheter using small incremental doses of bupivacaine 0.5% w/v as per routine clinical practice.

Once the anaesthetic block was deemed suitable for surgery to proceed, the patient was turned supine with left lateral tilt. Hartmann's solution 1–2 litre i.v. was administered during surgery at the discretion of the unblinded anaesthetist. If at any point the patient experienced discomfort a top-up of bupivacaine 0.5% w/v was administered via the epidural catheter, again using incremental doses. At the end of surgery all patients received epidural diamorphine hydrochloride 2.5 mg and rectal diclofenac sodium 100 mg for postoperative analgesia.

The anaesthetist assessing the block extent was blinded to the dose used and was not present during the part of the procedure when EVE was administered and therefore unaware of group allocation. Assessments were made at 5-min intervals. The anaesthetist who performed the CSE remained with the patient for the duration of the operation and treated any hypotension according to the study protocol. Any requirement for an epidural top-up before 45 min was also determined by the unblinded anaesthetist, in response to patients expressing intraoperative discomfort.

Age, weight, height, gestation, and parity were recorded. In addition data collected included maximum percentage drop in SAP, total ephedrine usage, or fluid volume infused (Table 3).

### Statistical analysis

Patient characteristics are expressed as mean (SD). The ED50 with 95% CI of intrathecal bupivacaine was estimated from the up-down reversals and by probit regression as a back-up or sensitivity analysis. Uppermost sensory block to touch, maximum percentage drop in SAP, total ephedrine usage and the amount of fluid given were analysed using Mann–Whitney U-tests. Analyses were carried out using the following software: Statview 5.01 (SAS Institute Inc.) statistical package, Excel 2000 (Microsoft Inc., Redmond, WA), Number Cruncher Statistical Software 2000 (NCSS, Inc., Kaysville, UT), Minitab 14 (Minitab Inc., State College, PA) and GraphPad Prism 4.01 (GraphPad Software Inc., San Diego, CA). Sample size estimations were based on an assumed standard deviation of 1.8 mg as one-fifth the range of likely doses (6–15 mg). Power was given at 0.8 to detect a difference of 2 mg significant at \( P<0.05 \) (two-sided). This produced an estimate of a minimum of 26 patients in each group.

### Results

Sixty patients were recruited. Eight were excluded: five because CSF could not be aspirated before intrathecal injection, two because the patients complained of dysaesthesia at the moment of dural puncture, and one because of protocol violation.

The patients’ characteristics were similar in the two groups (Table 1).

The sequences of effective and ineffective doses for both test groups are shown in Figure 1. The ED50 for hyperbaric bupivacaine 0.5% w/v with 25 µg fentanyl was 6.1 mg (95% CI 5.4–6.8) for the NEVE group and 5.1 mg (95% CI 4.0–6.1) with EVE from analysis of up-down reversals. This difference (1.0 mg, 95% CI –0.12 to 2.2, \( P=0.08 \)) was not statistically or clinically significant. The results of probit regression and ratio or effect sizes are presented in Table 2.

Analysing the data from parturients who received doses defined as successful, showed no differences in groups regarding maximum height of sensory block to touch, maximum percentage drop in SAP, ephedrine usage, or fluid volume infused (Table 3).

### Table 1 Patients’ characteristics. Results are expressed as mean (range) or mean (sd)

<table>
<thead>
<tr>
<th>Variable</th>
<th>NEVE (n=26)</th>
<th>EVE (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.1 (21–41)</td>
<td>33.2 (18–43)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.8 (11.3)</td>
<td>70.5 (8.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.3 (7.4)</td>
<td>164.0 (6.7)</td>
</tr>
</tbody>
</table>

### Table 2 ED50 heavy bupivacaine (mg) with 25 µg fentanyl. Results are presented as ED50 and ratio (95% CI)

<table>
<thead>
<tr>
<th>NEVE (n=26)</th>
<th>EVE (n=26)</th>
<th>Ratio</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-down analysis</td>
<td>6.1 (5.4, 6.8)</td>
<td>5.1 (4.0, 6.1)</td>
<td>0.84 (0.66, 1.03)</td>
</tr>
<tr>
<td>Probit regression</td>
<td>5.9 (5.1, 7.0)</td>
<td>4.8 (4.1, 5.8)</td>
<td>0.81 (0.64, 1.03)</td>
</tr>
</tbody>
</table>
This study has found the ED50 of intrathecal hyperbaric bupivacaine 0.5% w/v with 25 mg fentanyl to be 6.1 mg, and that EVE has no significant or reliable dose lowering effect. Therefore, there does not appear to be any advantage of using EVE in this situation.

Previous studies showing an effect of EVE have done so by demonstrating an increased cephalad spread of the initial intrathecal injection. Blumgart and colleagues injected bupivacaine 0.5% w/v 10 ml or saline 0.9% w/v 10 ml epidurally, 5 min after intrathecal injection, and showed a similar increase in sensory block height of four dermatomal segments compared with the control group. They concluded that this EVE effect was primarily a volume effect, which is why we used saline 0.9% w/v in our study rather than local anaesthetic. Other studies have used non-obstetric patients. Stienstra and colleagues using volumes of 5 and 10 ml saline 0.9% w/v and Mardirosoff and co-workers using 10 ml saline 0.9% w/v showed an increase in maximal sensory block of two segmental levels. In our study all patients received varying doses of intrathecal bupivacaine according to up-down sequential allocation and consequently this methodology would not be expected to demonstrate an extension of the block height with EVE. The purpose of our study was to establish whether EVE might enable anaesthesia to be provided with a decreased dose of local anaesthetic.

The findings of a previous study may have demonstrated such an effect. Parturients were randomized into two groups. They received either intrathecal hyperbaric bupivacaine 9 mg with fentanyl 10 µg or intrathecal hyperbaric bupivacaine 5 mg with fentanyl 10 µg followed by saline 0.9% w/v 6 ml through an epidural catheter. Both groups had similar quality of anaesthesia for Caesarean section but the EVE group demonstrated a faster motor recovery. The authors concluded that these findings were a result of an effect of EVE. However, they acknowledge that the interpretation of the findings is limited because no control group of patients receiving bupivacaine 5 mg with fentanyl 10 µg without EVE was included. As previous studies have shown, and our study confirms, it is possible to provide anaesthesia for Caesarean section with relatively low intrathecal doses without the need for EVE. Therefore, the findings of Lew and colleagues may also be explained by the use of different intrathecal dosages of bupivacaine rather than an effect of EVE.

We were unable to show a significant intrathecal dose lowering effect with EVE in our study. This may be because the use of heavy bupivacaine as opposed to plain may have reduced the effects of EVE. However, Yamazaki and colleagues detected no difference in the augmenting effect of 8 ml EVE with isobaric or hyperbaric tetracaine in non-obstetric patients. It is also possible that the epidural injection of 7 ml was insufficient to cause compartmental compression. We think this is unlikely as Takiguchi and colleagues in their myelographic studies demonstrated an effect with only 5 ml EVE and other studies have shown effects with 6, 8 and 10 ml. We chose a dose of 7 ml saline 0.9% w/v also for practical reasons—this being the usual volume left in the syringe having used a loss of resistance to saline technique for the epidural component of the CSE.
With no significant difference between the two groups regarding ED50 it is unsurprising that maximum height of sensory block to touch, maximum percentage drop in SAP and ephedrine usage between the two groups were similar.

We defined successful anaesthesia as achieving a sensory block to touch to the level of the xiphisternum. To provide anaesthesia with regional techniques, Aβ fibres as well as Aδ and c fibres must be blocked, and this can be tested using touch. The dermatomal height of the block was determined using ethyl chloride spray by asking patients when they first felt the sensation of the spray on their skin. It has been shown that using ethyl chloride spray in this way is equivalent to testing for touch with pin prick.10 The level of the xiphisternum was chosen in accordance with recommendations to achieve a block to T5 to touch to prevent pain during Caesarean section.11

In this study, for a dose to be defined as successful it not only had to achieve a sensory block to the xiphisternum, but it also had to provide anaesthesia for at least 45 min post-intrathecal injection. We felt this was a reasonable expectation of duration of surgery, however we acknowledge that in situations where surgery is expected to take longer, a higher intrathecal dose might be needed or anaesthesia may need to be extended using epidural top ups.

The unblinded anaesthetist who performed the CSE remained with the patient to support them throughout their Caesarean section. This anaesthetist therefore determined arterial pressure management and assessed when a top up was required. Although this is a limitation in the study, arterial pressure management was directed by a clear protocol and results were not significantly different between the two groups. With regard to the determination of epidural top up requirements, of the 22 doses that were defined as unsuccessful, 17 were because the intrathecal injection failed to achieve the required block height before surgery commenced and this was assessed by a blinded anaesthetist. We therefore do not think that this limitation in study design altered the overall findings of the study.

This study had 91% power to detect a minimum difference of 2 mg as significant in the two groups. A minimum of 2 mg eventually represented approximately a 33% reduction in dose and was considered clinically significant for the purposes of this study. The 1 mg difference found represents a dose reduction of less than 20%. The study had only approximately 40% power to find a 1 mg difference as significant and the sample size would need to be increased by a factor of 2.7, requiring approximately 140 evaluable subjects to achieve 80% power. Whilst the 1 mg difference and 95% CI (0.12 to 2.2) found does not exclude the possibility of a difference of 2 mg or greater, the probability is only 0.06 for this eventuality. We chose not to power the study for a difference of 1 mg because in practical terms this small reduction in dose would not be clinically important.

In conclusion, we estimated the ED50 of intrathecal bupivacaine with 25 μg fentanyl for Caesarean section to be 6.1 mg. Providing a CSE technique is used, anaesthesia for Caesarean section can be achieved with low doses of intrathecal bupivacaine and fentanyl. However, EVE proved ineffective in achieving further significant or reliable reductions in dosing requirements for intrathecal bupivacaine.

References