COMPARISON OF FOUR LOCAL EXTRADURAL ANAESTHETIC SOLUTIONS FOR ELECTIVE CAESAREAN SECTION†

P. HOWELL, W. DAVIES, M. WRIGLEY, P. TAN AND B. MORGAN

SUMMARY
We have examined a combination of two local anaesthetics to see if the resultant solution is superior to the agents individually. This study shows that a mixture of bupivacaine and lignocaine provided an excellent alternative to bupivacaine alone, and was superior to 2% lignocaine with adrenaline for elective Caesarean section. By reducing the dose of bupivacaine used, the combination may reduce the risk of cardiotoxicity.

KEY WORDS

Extradural anaesthesia is a popular technique for Caesarean section and is preferred to general anaesthesia by many patients. Its use has been advocated as the technique of choice in the latest report on maternal deaths as it avoids the risks of general anaesthesia [1].

Paramount amongst the requirements of extradural anaesthesia are maternal and fetal safety, followed closely by reliability of the block. The ideal agent would produce a block of rapid onset, good quality and adequate duration, with a minimum of toxic effects to mother or baby.

Plain 0.5% bupivacaine solution has been the standard agent for Caesarean section in the U.K. for many years, but the addition of 1:200000 adrenaline has been shown to improve the efficacy of the block [2] and to prolong its duration of action [3]. Reynolds, Hargrove and Wyman showed that the addition of adrenaline reduced the maternal plasma concentration of bupivacaine during labour [4], although this was not the finding of Wilson and colleagues at Caesarean section [3]. Lignocaine 2% has been used widely in the U.S.A. Early reports that it caused neonatal depression [5] have not been substantiated, and Abboud and her co-workers have shown 2% lignocaine was a safe and effective alternative to 0.5% bupivacaine, especially when adrenaline 1:200000 was added [6]. The same workers found that the onset of action of plain lignocaine was delayed by addition of adrenaline, but that the quality of the block was improved.

Mixtures of local anaesthetic agents have been used for several years in non-obstetric practice, to utilize the beneficial properties of both agents. In addition, reducing the dose of bupivacaine may reduce the risk of its cardiotoxicity [7].

We have compared a 50:50 mixture of 2% lignocaine and 0.5% bupivacaine with adrenaline (“the mixture”) with the three other solutions in common use in the U.K., to determine if the onset time or quality of block produced by the mixture showed any clinical advantages.

PATIENTS AND METHODS
We studied 80 healthy women presenting for elective Caesarean section under extradural anaesthesia after Ethics Committee approval and informed patient consent had been obtained. Mothers with pre-eclampsia or pre-term delivery were excluded. The extradural catheter was introduced using a 22G Tuohy needle at L2/3 or L3/4, and the mixture or one of the other solutions was injected under real-time monitoring of the block. The patients were observed for 48 hours post-operatively to monitor for any complications.

We have found that the mixture provided rapid onset, good quality and adequate duration, with a minimum of toxic effects to mother or baby. In addition, reducing the dose of bupivacaine may reduce the risk of its cardiotoxicity [7].

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eries were excluded. Subjects were allocated randomly to receive one of the four solutions under study: 0.5% bupivacaine plain (B), 0.5% bupivacaine with 1:200 000 adrenaline (B + A), 2% lignocaine with 1:200 000 adrenaline (L + A), or a 50:50 mixture of 0.5% bupivacaine and 2% lignocaine with 1:200 000 adrenaline (mixture). Adrenaline was added freshly to the plain preservative-free solutions, where appropriate, as 0.1 ml of 1:1000 adrenaline to each 20 ml, in order to keep the pH of each solution similar. The mixture was made up by adding 10 ml of plain 0.5% bupivacaine to 10 ml of plain 2% lignocaine, and adding adrenaline as described. All solutions were used at room temperature, and there was no attempt to adjust the pH. A maximum of 40 ml of test solution was available to each patient.

The study was performed in a double-blind manner, and each solution was prepared freshly by a second anaesthetist who was not involved directly in the anaesthetic or testing of the patient.

Following routine prophylaxis with ranitidine and oral antacid, cannulation of a vein and non-invasive cardiovascular monitoring, the patient was placed in the left lateral position. The extradural space was located by a 16-gauge Tuohy needle at the L2–3 or L3–4 interspace with the loss of resistance to saline technique, and 3 cm of catheter was left in the space.

After an i.v. preload of Hartmann’s solution 1 litre, 3 ml of the test extradural solution was injected through the catheter with the patient in the left lateral position. After 5 min, with no sign of catheter misplacement, a further 17 ml of test solution was injected over 2 min. Five minutes after the end of this main injection, the patient was turned to the right lateral position. Arterial pressure and heart rate were recorded every 5 min, as was the progress of the block. Sympathetic block was assessed by the presence of warm and vasodilated feet, sensory block by the loss of cold sensation with ethyl chloride spray, and motor block by loss of leg muscle power on a four-point Bromage scale. If, 20 min after the end of the main injection, the thoracic or sacral sensory level was considered inadequate, further increments of the same solution were given and the patient’s position changed, as deemed appropriate.

In all patients ephedrine 60 mg was added to the second 1 litre of Hartmann’s solution. Hypotension was minimized by infusing this solution to ensure that the systolic arterial pressure was maintained greater than 100 mm Hg or more than 80% of the pre-extradural value.

Surgery was permitted only when the anaesthetist considered that the block was adequate in density and spread. An upper sensory level of T4 and a lower level of S5 were considered appropriate. The onset time was defined as the time from giving the test dose to the patient being ready for surgery, as assessed by the anaesthetist. Any pain or discomfort during the procedure was treated by inhalation of Entonox (a 50:50 mixture of oxygen and nitrous oxide), supplementary extradural solution, or i.v. or extradural opioids after delivery of the baby.

Maternal blood samples were taken also at specific times, for measurement of plasma concentrations of local anaesthetic, as was cord blood at delivery.

The progress of motor and sensory blocks was checked at 1-h intervals in the postoperative period, and the mothers were given extradural diamorphine analgesia (0.06 mg kg⁻¹, to a maximum of 5 mg) when the upper sensory level had regressed by three segments. One hour after the end of surgery, both anaesthetist and patient were asked to answer preset questions to evaluate the extradural.

Statistical analysis

To compare the four anaesthetic groups, analysis of variance techniques were used. For continuous variables the parametric form was used, but for discrete variables the non-parametric Kruskal-Wallis analysis of variance was used. A chi-square test was also used where appropriate. \( P < 0.05 \) was regarded as statistically significant.

RESULTS

The groups were comparable for patient age (mean 33.0 (SD 5.1) yr) and weight (77.0 (SD 12.1) kg), and duration of surgery (mean 47.1 (SD 10.5) min).

There was no significant difference in the volumes of extradural solution used in each group (B: 24.2 (SD 4.3) ml; B + A: 22.3 (SD 3.7) ml; L + A: 26.4 (SD 7.2) ml and mixture: 23.5 (SD 5.4) ml). The overall mean volume used was 24.0 (SD 5.5) ml. Fewer patients given bupivacaine with adrenaline or the mixture required supplementary top-ups than in the other groups, although the difference was not significant (fig. 1). There was no symptomatic evidence of systemic toxicity in any patient.
There was no difference between the four solutions in the time to provide adequate anaesthesia for surgery (mean onset time to surgical block 24.6 (SD 7.4) min): group B, 26.5 (SD 7.2) min; group B + A, 26.4 (SD 7.2) min; group L + A, 23.2 (SD 7.6) min and mixture, 22.4 (SD 6.6) min.

There were no excessively high blocks in any group, although four patients showed signs of sensory block up to C7 or C8 level. There was no difference between groups in terms of the maximum height achieved, and four patients had blocks up to T5 or T6.

**FIG. 1.** Number of patients in each group requiring supplementary top-ups.

Surgery was possible in all patients under extradural anaesthesia, and none of the patients required or requested conversion to general anaesthesia. However, one patient in the lignocaine group had inadequate sensory block (patchy S1–T7) after 40 ml had been given, and surgery was possible only after an additional 10 ml of plain 0.5% bupivacaine. The results from this patient were therefore withdrawn from the study.

Sixty-six percent (52/79) of patients felt no pain at all. However, more pain was experienced by patients given lignocaine, as a significantly smaller number of patients in this group said they had had pain-free surgery (P = 0.02) (table I).

Although none of the patients described pain as severe, supplementary opioid analgesia was required by 13 patients (table I). Those in the lignocaine group required significantly more supplementary opioids than those given the other solutions (P < 0.05).

When the patients were asked how satisfactory they had found the extradural for their Caesarean section, 86% (68/79) stated it to have been

<table>
<thead>
<tr>
<th>TABLE I. Number of patients in each group experiencing pain or discomfort during their Caesarean section. *P &lt; 0.05 compared with other groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>None</td>
</tr>
<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

**TABLE II.** Number of patients in each group requiring supplementary analgesia during Caesarean section.

*P < 0.05 compared with other groups

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine (n = 20)</th>
<th>Bupivacaine + adrenaline (n = 20)</th>
<th>Lignocaine + adrenaline (n = 19)</th>
<th>Mixture (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.v. fentanyl</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Extradural diamorphine</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Entonox</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Topical lignocaine</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>2</td>
<td>7*</td>
<td>2</td>
</tr>
</tbody>
</table>
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FIG. 2. Percent of patients (■) and anaesthetists (□) who considered the quality of block produced by each solution was excellent or very good.

TABLE III. Assessment by the patients and anaesthetists of the extradural block produced by the four local anaesthetic solutions. No significant difference between groups

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine (n = 20)</th>
<th>Bupivacaine + adrenaline (n = 20)</th>
<th>Lignocaine + adrenaline (n = 20)</th>
<th>Mixture (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>12 (10)</td>
<td>12 (15)</td>
<td>9 (10)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Very good</td>
<td>4 (3)</td>
<td>8 (3)</td>
<td>5 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Good</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fair</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0 (2)</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

excellent or very good (fig. 2). Only one patient considered her extradural to have been poor, and no significant difference was shown between the groups as assessed by either patients or anaesthetists. All 20 patients who received bupivacaine with adrenaline stated that the extradural was excellent or very good (table III). It is interesting to note, however, that the anaesthetists were uniformly unable to identify which of the four solutions was used.

There was no difference between groups in overall duration of sensory block. The mean time taken for the upper sensory level to regress by three segments measured in 12 patients in each group was 151 (SD 41) min (B: 152 (SD 35) min; B + A: 163 (SD 43) min; L + A: 135 (SD 41) min; mixture: 150 (SD 40) min). In addition, the duration of motor block was similar with all four solutions, with a mean duration of 195 (SD 75) min. More than 80% of patients in each group developed a motor block of Bromage grade 2 or 3.

Following the initial preload of crystalloid solution 1 litre, only five patients received no further fluids or ephedrine. In the remainder of the patients, an ephedrine infusion was used. The mean dose of ephedrine infused during the procedure was 29.1 (SD 19) mg, and there was no significant difference between the groups in the doses given (B: 35.4 (SD 20) mg; B + A: 23.0 (SD 10) mg; L + A: 30.0 (SD 23) mg; mixture: 28.0 (18) mg).

The pH of freshly prepared test solutions was measured on a Whatman PHA 250 apparatus, as was a commercial preparation of 0.5% bupivacaine with 1:200000 adrenaline (Astra Pharmaceuticals Ltd) (table IV).

All the babies delivered in this study were in good condition and had Apgar scores greater than 7 at 1 min and 9 or more at 5 min. None required resuscitation.

TABLE IV. pH of samples of each extradural solution used compared with a commercial preparation as tested on a Whatman PHA 250 apparatus

<table>
<thead>
<tr>
<th>Extradural solution</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>5.66</td>
</tr>
<tr>
<td>Bupivacaine + adrenaline</td>
<td>5.41</td>
</tr>
<tr>
<td>Lignocaine + adrenaline</td>
<td>4.81</td>
</tr>
<tr>
<td>Mixture</td>
<td>4.91</td>
</tr>
<tr>
<td>Commercial 0.5% bupivacaine + adrenaline (Astra Pharmaceuticals Ltd)</td>
<td>3.16</td>
</tr>
</tbody>
</table>
DISCUSSION

We found no difference in onset times between the agents used, and in particular lignocaine either alone or in the mixture did not work significantly faster than the bupivacaine solutions. With comparable solutions, our onset times are almost identical to those of Abboud and co-workers [6] and Laishley and Morgan [2], but faster than those in studies by Paech [8] and especially by Wilson and co-workers [3]. However, in the latter two studies, a slow incremental technique was used, and this would be expected to produce a block of slower onset. After performing a 3-ml test dose, we chose to give the whole of the 17-ml main dose as a slow continuous injection over 2 min. We consider this is safe, provided continuous observation of the patient is maintained during the injection. Inadvertent i.v injection should be detectable early by asking the patient to report unusual sensations during the slow injection itself. In addition, continuous ECG and automated arterial pressure recording are mandatory to provide objective warning of cardiovascular toxicity. We were ready to prevent hypotension by using an infusion of ephedrine after the initial 1-litre preload, as has been suggested by Datta and colleagues [9] and Yang, Abouleish and Caritis [10]. There has been much debate on the relative benefits of fluid infusion or vasoconstrictors, but the use of a vasoconstrictor such as ephedrine has been proposed recently as the most appropriate management [11].

Mixtures of bupivacaine and lignocaine have been used in non-obstetric situations with varied results. Magee, Sweet and Holland showed in surgical patients that the mixture produced sensory block of more rapid onset than that of bupivacaine alone [12]. However, Seow and colleagues found that, when solutions with adrenaline were used, the mixture produced marked motor block but there was no difference in onset times of sensory block compared with the individual agents [13]. We were unable to find any such differences in our obstetric patients.

Using a combination of chloroprocaine and bupivacaine for brachial plexus block, Cunningham and Kaplan found the time to maximum anaesthesia was halved compared with that of bupivacaine alone [14]. However, Cohen and Thurlow found no advantages in combining these two agents for extradural analgesia in labour [15]. To our knowledge, this is the only report of mixtures being used in obstetric patients.

In previous studies, the quality of the block produced by lignocaine with adrenaline was considered similar to that of bupivacaine, with or without adrenaline [8, 15]. However, we found that the block produced by lignocaine was substantially worse \( (P < 0.05) \) than that of all the other solutions tested, as more pain was experienced by the patients in this group, and more opioid supplementation was required. In addition, we had one seriously inadequate block which required supplementation with bupivacaine. Hence, contrary to the conclusions of Norton, Davies and Spicer [16], we found no advantage in the use of 2% lignocaine with adrenaline for Caesarean section, and indeed consider that it is unsuitable for this type of surgery. However, this should be distinguished from the use of 2% lignocaine with adrenaline to supplement a pre-existing bupivacaine extradural—an effective technique which is used commonly in this establishment.

Similar volumes of extradural solution were used in each group; this suggests that the four solutions were equipotent. The mixture worked as well as both bupivacaine solutions in providing good overall conditions for surgery, and both patient and anaesthetist satisfaction was high with this combination. The addition of bupivacaine to the lignocaine solution improved the quality of block produced. Although not statistically significant, there was a trend which suggested that bupivacaine with adrenaline performed best in almost every variable tested; it is possible that a follow-up study with larger groups would confirm this.

The pH values of the solutions used were considerably less than expected, although none was as low as that of the commercially prepared solution of bupivacaine with adrenaline. These are all much lower than the \( pK_a \) of bupivacaine or lignocaine, and this would result in a small proportion of the agents being present in the unionized form in solution. As this is the form which penetrates the nerve, and hence produces the effect, sub-optimal results may be expected. The adjustment of pH by adding sodium bicarbonate to each solution may have improved efficacy [17, 18].

The toxicity of local anaesthetics is reflected in the median convulsant dose, the \( CD_{50} \), and the median lethal (cardiotoxic) dose, the \( LD_{50} \). With bupivacaine, the safety window between these two values is small, in contrast with lignocaine, with which there is a wider difference [19]. Albright,
amongst others, has pointed to the possible specific cardiotoxicity of bupivacaine compared with equipotent doses of other agents [7]. Reiz and Nath showed that bupivacaine was four times more potent than lignocaine in depressing myocardial contractility in pigs, but 16 times more potent in prolonging the QRS interval, which is a frequent antecedent of fatal ventricular fibrillation [20]. Interestingly, lignocaine has been used successfully in cats to treat bupivacaine-induced ventricular arrhythmias [21]. The toxicity of mixtures of amide local anaesthetics is poorly understood, and animal work suggests that it may be additive [19, 22]. However, De Jong and Bonin showed that the addition of lignocaine to bupivacaine widened the window between the CD60 and the LD60, and concluded that convulsions from a bupivacaine–lignocaine mixture were less likely to terminate fatally than if bupivacaine were given alone [19].

ACKNOWLEDGEMENTS

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REFERENCES