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ORIGINAL ARTICLE

A comparison of epidural ropivacaine 0.75% and bupivacaine 0.5% with fentanyl for elective caesarean section

N. Christelis, J. Harrad, P. R. Howell

Departments of Anaesthetics, St. Mary's Hospital, London, County Hospital, Hereford and Homerton Hospital, London, UK

Background: Early studies suggested that ropivacaine had clinical advantages over bupivacaine with respect to cardiotoxicity and motor block, and that it was suitable for epidural caesarean section. This study was set up to compare epidural 0.75% ropivacaine with a popular bupivacaine/fentanyl mixture for elective caesarean section.
Methods: Eighty women having elective caesarean section under epidural anaesthesia were randomly allocated to receive 20 mL of either 0.75% ropivacaine or 0.5% bupivacaine plus fentanyl 100 μg. Supplementation with 2% plain lidocaine was used where necessary. Times were recorded for onset of sensory block, density and duration of motor block, and the need for supplementation.
Results: There was no difference between the groups in the time (mean [SD]) to achieve sensory blockade to cold to T4 (ropivacaine 15.8 [5.6] min, bupivacaine/fentanyl 18.7 [9.1] min, $P = 0.13$) or to S1 (ropivacaine 18.3 [4.6] min, bupivacaine/fentanyl 17.4 [7.6] min, $P = 0.59$), or in the need for supplementation. However, ropivacaine produced a motor block that was denser (median Bromage score ropivacaine 3, bupivacaine/fentanyl 1.5, $P = 0.0041$), and of longer duration (ropivacaine 237 [84] min, bupivacaine/fentanyl 144 [76] min, $P < 0.0001$).
Conclusions: This study suggests that epidural 0.75% ropivacaine without opioid may be used as an alternative to bupivacaine 0.5% with fentanyl for elective caesarean section, but it does not induce anaesthesia any faster and may result in a denser, more prolonged, motor block.

Keywords: Anaesthesia, obstetrical; Anaesthesia, epidural; Caesarean section; Anaesthesia, local: bupivacaine; Anaesthesia, local: ropivacaine

INTRODUCTION

Regional anaesthesia is widely considered the technique of choice for caesarean section, and although *de novo* epidural anaesthesia is currently much less popular than spinal anaesthesia, it is still an important technique.[1]

Of all the solutions in use for providing *de novo* epidural anaesthesia in the UK, the most popular is probably a mixture of 0.5% bupivacaine with fentanyl 50–100 μg. Lidocaine 2% plain or with epinephrine (popular in North America) is rarely used as a first line agent in the UK. However, any mixture of bupivacaine and fentanyl is unlicensed, and since it is not commercially available, needs to be made up on an individual basis. This task is time-consuming and increases the risks of contamination or drug administration errors.

Ropivacaine 0.5% has been shown to be an effective agent for providing epidural anaesthesia for caesarean section, providing similar, satisfactory conditions to 0.5% bupivacaine.[2–4] Other workers have used 0.75% ropivacaine and also found it to be effective.[5–6] Irestedt and colleagues showed that 20 mL of 0.75% ropivacaine was enough to provide satisfactory conditions for caesarean, and preferable to the higher dose of 25 mL that produced excessively high sensory blockade.[5]

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N. Christelis, Department of Anaesthetics, St. Mary's Hospital, London, **J. Harrad,** Department of Anaesthetics, County Hospital, Hereford, **P.R. Howell,** Department of Anaesthetics, Homerton Hospital, London, UK.

Correspondence to: Dr Nick Christelis, Department of Anaesthetics, St. Mary's Hospital, Praed Street, London W2 1NY, UK.
E-mail: nick.christelis@doctors.org.uk

This study was set up to investigate how plain 0.75% ropivacaine (licensed for epidural use in the UK), compared to the popular (unlicensed) bupivacaine-fentanyl mixture when establishing *de novo* epidural block for elective caesarean section. The primary aim was to ascertain if there was any difference in speed of onset between the two solutions, and secondary aims were to compare the success and quality of sensory blockade, and the extent and duration of motor blockade.

METHODS

Following ethics committee approval, this double-blind randomised controlled trial was undertaken at Homerton Hospital. Statistical advice had been sought in the planning stage and power analysis suggested that 32 patients were required in each group to detect a 5-min difference in onset time of sensory blockade (80% power, $P < 0.05$). Eighty pregnant women booked for elective caesarean section were recruited and gave written informed consent. All women were ASA I or II, at $\geqslant 36$ weeks of gestation with a singleton fetus, and over 18 years old. Women in labour, those unable to communicate in English, those who had had significant back surgery, injury or scoliosis, and those known to have an allergy to amide local anaesthetics were excluded. Women in whom there was any concern about fetal well-being were also excluded.

All women were premedicated with oral ranitidine 150 mg and metoclopramide 10 mg. On arrival in the theatre suite they were given 25 mL of 0.3 M sodium citrate orally. Hartmann's solution 1000 mL was given intravenously. The epidural was performed by either a consultant anaesthetist or a trainee with the patient in the sitting or lateral position. The epidural space was identified according to normal practice in the L2-3 or L3-4 interspace with a 16-gauge Tuohy needle, bevel cephalad, using a midline approach, with loss of resistance to either air or saline. An epidural catheter was inserted with 3 cm left in the epidural space, and subjects were then positioned supine with approximately 15° uterine tilt to the left (ensuring that the abdominal bump *looked* displaced), and 5° head-up.

A second anaesthetist, not involved in the study, prepared and administered the study solution according to instructions found within a pre-randomised, sealed, numbered envelope. Subjects were randomly allocated to receive either 20 mL of 0.75% ropivacaine (group R) or 20 mL of 0.5% bupivacaine plus fentanyl 100 μg (group BF). The hubs of the 20-mL syringes were covered with opaque tape to prevent the investigators detecting the difference in volumes administered (20 mL vs. 22 mL). Five minutes after a 3-mL test dose of 2% plain lidocaine had been given by the investigator, the study solution was given by the second anaesthetist who then left the theatre and took no further part in the case. The solution was given slowly over 2 min whilst maintaining verbal communication with the patient. All assessments (preoperative, intraoperative and postoperative) were made by the investigators who were unaware of which epidural solution had been administered. The timing period for the study began once all the study solution had been given.

Electrocardiogram (ECG) and pulse oximetry were started upon arrival in theatre. An automated sphygmomanometer recorded maternal arterial pressures every 5 min. All women received a further 1000 mL of Gelofusin during surgery. Hypotension (systolic pressure <100 mmHg, or a 20% drop from baseline, or symptoms of nausea, dizziness or faintness) was treated using additional fluids and/or ephedrine 3–6 mg boluses.

The extent of sensory blockade was determined using ethyl chloride spray and checked every two minutes until surgery began. Recorded times included the time to achieve bilateral T4 to S1 sensory blockade, and the time the anaesthetists considered the patient ready for surgery ('ready for surgery' time). In line with clinical practice, surgery was not allowed to start until bilateral T4 to S1 sensory blockade and bilateral sympathetic blockade (warm, dry feet) were demonstrated.

If the sensory block was inadequate 20 min after the study solution had been given, or if the patient required intraoperative supplementation of the block, 2% plain lidocaine was given via the epidural route to a maximum of 10 mL. However, if more than 10 mL of 2% lidocaine was required for supplementation the subject was withdrawn from the study and received either spinal or general anaesthesia.

Bilateral motor block was assessed immediately before surgery, at the end of surgery and every 30 min postoperatively until full regression had occurred. A modified four-point Bromage scale was used (grade 0 = able to move hips, knees, feet and lift legs up, grade 1 = able to move knees and feet, grade 2 = only able to move feet, grade 3 = unable to move hips, knees or feet).

During surgery, all women received oxygen ($6\ \mathrm{L\ min^{-1}}$) via a Hudson mask until delivery of the baby, whereupon Syntocinon 10 units (in two divided doses) and a single dose of antibiotics (co-amoxiclav 1000 mg/200 mg) were given intravenously. Assessment of the baby, according to obstetric protocol, included routine preoperative fetal heart monitoring using a cardiotocograph, Apgar scores at 1, 5 and 10 min after delivery and umbilical cord gas analysis.

The postoperative analgesic regimen used for all women was standard for this hospital at the time of the study. This comprised intravenous morphine via a patient-controlled device (bolus morphine 1 mg, lockout time 5 min, no background infusion), as well as

paracetamol (1 g four times daily) and diclofenac (50 mg three times daily) regularly.

In the recovery room, subjects were asked to comment on any pain or discomfort they had felt during surgery (none, mild, moderate or severe), and whether they felt itchy at all (none, mild or severe). The investigating anaesthetist was asked how effective they considered the epidural to have been (poor, fair, good or excellent). Twenty-four hours after surgery subjects were asked similar questions about their recall of intraoperative pain and discomfort, or itchiness.

Advice from a university lecturer in statistics had been sought in the design of the study, and data were analysed using two-tailed Student t, χ^2, Fisher's exact and MannWhitney tests as appropriate using the following software: Excel 2000 (Microsoft Corp., Redmond VA) and Number Cruncher Statistical Systems (NCSS) 2000 (NCSS Inc., Kaysville UT). A value of $P < 0.05$ was considered statistically significant.

RESULTS

There were no statistically significant differences between the two groups with respect to pre-test variables such as patient characteristics or technical issues relating to siting the epidural. A flow chart (Fig. 1) summarises the outcome of patients following administration of the study solutions.

In group R, 30 women developed a bilateral T4-S1 sensory block after just the initial bolus dose of epidural study solution, and two women were removed from the study due to an obviously inadequate block. Six women were given additional boluses of 2% lidocaine. One of these women never achieved a satisfactory T4-S1 block, and was subsequently given spinal anaesthesia. Two women in group R "collapsed" during or immediately after injection of the initial bolus dose and were withdrawn due to suspected intravascular placement of the epidural catheter (one turned out to be a transient vasovagal faint – *vide infra*). Surgery was therefore allowed to start in 35 women in group R, and seven of these required intraoperative supplementation according to the protocol. Four of these women were subsequently removed from the study due to intraoperative discomfort, two continuing under epidural analgesia but requiring protocol-breaking supplementation, and two requiring conversion to general anaesthesia.

In group BF, 26 women achieved a T4-S1 sensory block after the initial bolus dose alone and the other 14 required additional boluses of 2% lidocaine. Three of these women were removed from the study since they did not achieve a T4-S1 block despite 10 mL of 2% lidocaine; they received spinal anaesthesia. Surgery was

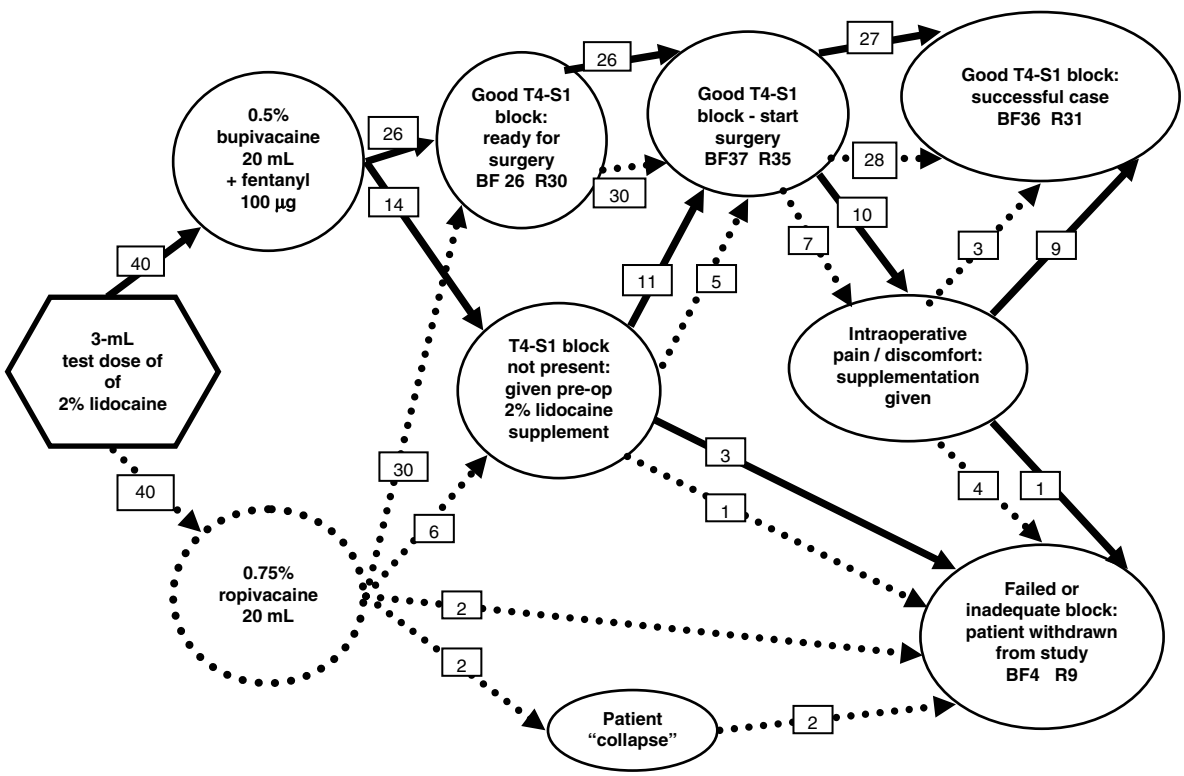

Fig. 1 Flowchart depicting the progress and outcome of women in the study. The figures in square boxes represent the number of subjects; BF = bupivacaine/fentanyl group; R = ropivacaine group.

therefore allowed to start in 37 women in group BF, and intraoperative supplementation was required by ten women, one of whom was taken out of the study as she required protocol-breaking supplementation for intraoperative pain.

Analysing the data, there was no significant difference between the two local anaesthetic solutions in the time taken to achieve bilateral T4 or S1 sensory block, or to be ready for surgery (Table 1). However, the density of motor blockade at the start of surgery was greater in group R than group BF ($P = 0.0041$) (Fig. 2), and there was a highly significant difference in the duration of motor blockade, taking much longer to wear off completely in group R compared to group BF (R 237 ± 84 min, BF 144 ± 76 min, $P < 0.0001$). When analysed separately, the data for the subset of 46 women who required nothing but the test dose and study solution showed similar results (Table 1), with no difference in time to achieve T4 sensory block, but a denser motor block in group R at the start of surgery ($P = 0.018$) (Fig. 3), and a significantly prolonged motor block ($P = 0.00046$) in group R.

There were no differences between the groups in duration of surgery, exteriorisation of the uterus, estimated blood loss, or sterilisation procedure (Table 2). Slightly more intravenous fluids were administered in group R (2250 mL) compared to group BF (2034 mL) ($P = 0.03$), and there was a trend to greater ephedrine usage in group R, but this did not reach statistical significance ($P = 0.07$). Neonatal outcome was good in both groups, with only three babies delivered with Apgar scores <7 at 1 min; all babies had Apgar scores ⩾8 at 5 min, and 10 at 10 min after delivery. There was no difference in neonatal umbilical artery pH values (Table 2).

Immediately after surgery, in the recovery room, there was no difference between the groups in qualitative assessments of intraoperative pain (Table 3), nor in the anaesthetists' assessment of epidural success (87% of epidurals in group R were rated "excellent" or "good" compared to 75% in group BF, $P = 0.60$)

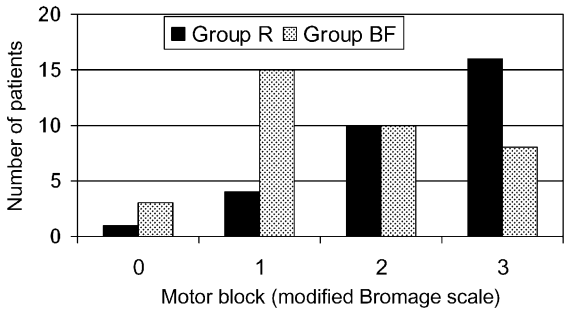

Fig. 2 Motor block immediately before surgery.

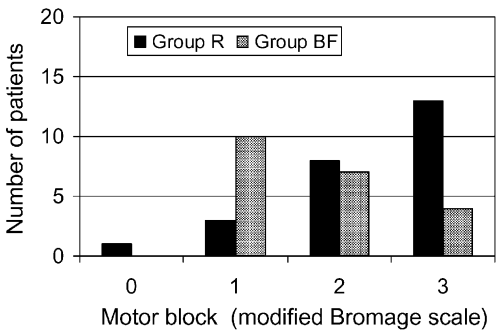

Fig. 3 Motor block immediately before surgery in the subset of women in whom no supplementation was required, so they received only the study drugs.

(Table 3). Twenty-four hours after surgery, women in group BF recalled having had more intraoperative pain and discomfort than those in group R ($P = 0.04$) (Table 3). Only one patient admitted to pruritus in the recovery room, and although the recall of pruritus had increased by 24 h after surgery, there was no difference in incidence between the groups (R 27%, BF 31%, $P = 0.75$), and only two women in each group considered the itching was severe. There was no difference in the 24-h consumption of intravenous morphine via a patient-controlled device (R 27.7 ± 18.6 mg, BF 30.3 ± 17.9 mg, $P = 0.56$).

Table 1. Sensory and motor block in all women who achieved a satisfactory T4-S1 sensory block, (including data for subset of women who did not require additional lidocaine supplementation to achieve T4-S1 sensory block)

	All patients group R ($n = 31$)	All patients group BF ($n = 36$)	*P* value	No additional lidocaine group R ($n = 25$)	No additional lidocaine group BF ($n = 21$)	*P* value
Time to T4 sensory block (min)	15.8 (5.6)	18.7 (9.1)	NS	14.8 (5.0)	14.1 (5.0)	NS
Time to S1 sensory block (min)	18.3 (4.6)	17.4 (7.6)	NS	18.2 (4.9)	14.3 (5.0)	0.012
"Ready for surgery" time (min)	19.4 (5.1)	21.2 (8.5)	NS	18.9 (5.0)	16.7 (4.6)	NS
Additional lidocaine for T4-S1 block (mg)	12.6 (31.5)	35.7 (63.1)	NS	n/a	n/a	
Motor block at start of surgery (Bromage Scale)	3 (2–3 [0–3])	1.5 (1–2 [0–3])	0.0041	3 (2–3 [0–3])	2 (1–2 [1–3])	0.018
Total additional lidocaine (mg)	27.7 (63.0)	55.6 (75.5)	NS	n/a	n/a	
Duration of motor block (min)	237 (84)	144 (76)	$P < 0.0001$	234 (86)	148 (14)	0.00046

Values are mean (SD) or median (IQR [range]).

Table 2. Intraoperative data for all women who achieved a satisfactory T4-S1 sensory block

	Group R ($n = 31$)	Group BF ($n = 36$)	P value
Incidence of hypotension	17 (55%)	20 (56%)	NS
Ephedrine use (mg)	10.3 (16.1)	4.9 (6.6)	0.07
Volume of i.v. fluids administered (mL)	2250 (433)	2034 (385)	0.03
Intra-operative blood loss (mL)	601 (264)	582 (293)	NS
Duration of surgery (min)	40.4 (14.3)	40.3 (13.8)	NS
Exteriorisation of uterus performed	7 (23%)	2 (6%)	0.07
Sterilisation performed	6 (19%)	2 (6%)	NS
1 min Apgar < 7	2 (6%)	1 (3%)	NS
Neonatal umbilical artery pH	7.30 (0.063)	7.31 (0.037)	NS

Values are mean (SD), median (IQR [range]) or number (proportion).

Table 3. Patient assessments of the severity of intraoperative pain and discomfort immediately after the operation, and 24 h later

	In recovery room group R ($n = 31$)	In recovery room group BF ($n = 36$)	24 h post-op group R ($n = 30$)[a]	24 h post-op group BF ($n = 33$)[a]
None	26 (84%)	26 (72%)	25 (83%)	19 (58%)
Mild	2 (6%)	4 (11%)	2 (7%)	6 (18%)
Moderate	3 (10%)	5 (14%)	2 (7%)	8 (24%)
Severe	0 (0%)	1 (3%)	1 (3%)	0 (0%)

Values are number (proportion).
[a]Follow-up data not available for all patients. There was a significant difference between groups R and BF 24 h post-op for severe pain and discomfort. $P = 0.04$.

DISCUSSION

When ropivacaine was first released it was widely promoted as a potentially superior agent to bupivacaine because of lower toxicity and less motor block. Animal studies suggested that ropivacaine is less cardiotoxic than bupivacaine, and in pregnant sheep it takes twice the dose of ropivacaine to cause circulatory collapse and death compared to bupivacaine.[7,8] Ropivacaine produces fewer arrhythmias than bupivacaine in the isolated perfused rabbit heart[9] and when given to human volunteers by intravenous infusion it was better tolerated, and associated with less reduction in myocardial contractility and conductivity than bupivacaine.[10,11] In addition, early clinical studies showed that ropivacaine 0.5% produced less motor blockade than bupivacaine 0.5%.[4,12–13]

The other great hope for ropivacaine was the separation of sensory and motor blockade. Studies in both obstetric and non-obstetric patients showed that epidural ropivacaine produced less intense and shorter lasting motor block than bupivacaine.[3–4,12–13] This has been widely hailed as a significant advantage for obstetric patients in whom motor block is both unnecessary and unwanted, particularly in labour.

However, several recent studies have challenged the validity of both these apparent benefits of ropivacaine. The development of the concept of minimum local anaesthetic concentration (MLAC) has suggested that ropivacaine, at least in weak concentrations as used for labour analgesia, is approximately 40% less potent than bupivacaine with respect to sensory block.[14–15] More recently, the same up-down sequential allocation technique has been used to demonstrate that the motor blocking potency of ropivacaine is similarly less than that of bupivacaine.[16] It is unclear whether these differences in potency apply when using stronger anaesthetic concentrations, but if this were the case, then having to use a larger dose of ropivacaine to achieve a satisfactory sensory block would erode much of the potential benefits of reduced cardiotoxicity and motor blockade. There have also been isolated reports of prolonged motor blockade.[17–19] Although this issue is arguably more important for women in labour than those undergoing operative delivery, persistent motor blockade may delay postoperative mobilisation, and is greatly disliked by patients.

In studies at caesarean section where epidural ropivacaine has been compared to bupivacaine, most have used 0.5% solutions in similar doses and found them equally effective.[2–4,20] Two studies have compared ropivacaine 0.75% with bupivacaine 0.5%. Veneziani and colleagues found ropivacaine 0.75% with fentanyl clinically superior to bupivacaine 0.5% with fentanyl using similar volumes (and consequently a 50% increase in dose).[21] Bjornestadt and colleagues found plain ropivacaine 0.75% equally effective as bupivacaine 0.5%, but with a similar 50% increase in dose of ropivacaine.[22] From these studies, which are largely underpowered to compare quality of sensory blockade, it is difficult to ascertain whether or not ropivacaine and bupivacaine are equipotent at this end of the concentration spectrum. However, both 0.5% and 0.75% ropivacaine appear to

be effective solutions for providing epidural anaesthesia for caesarean section.

One of the main stimuli for carrying out our study was a local clinical impression that plain ropivacaine 0.75% produced an effective epidural block more quickly than the usual alternative, bupivacaine 0.5% with fentanyl 100 μg. However, the results of our study do not support that contention, demonstrating similar onset times for sensory blockade. To our surprise, the main difference observed was that ropivacaine 0.75% is associated with a much longer-lasting motor block and more varied Bromage scores than the bupivacaine-fentanyl mixture, (Table 1, Figs. 2,3). In fact, the motor block from ropivacaine took about 60% longer to wear off.

Our data were analysed on a per-protocol basis, including all subjects whether or not they needed additional lidocaine to achieve a satisfactory block. Similar results were found when separate analysis was performed on the subset of patients who needed no supplementation of the study drugs; in other words, the results may be taken to reflect the true nature of the epidural solutions under test (Table 1). The only difference observed between this subset and the main dataset was that women in group BF achieved S1 sensory block 4 min faster than those in group R ($P = 0.012$).

No difference in the incidence of hypotension was detected between the groups. However, there was a suggestion that sympathetic blockade needed more aggressive management in the ropivacaine group; slightly more intravenous fluids were required, as well as a greater dose of ephedrine, although this did not reach statistical significance.

Evidence suggests that ropivacaine is less cardiotoxic than bupivacaine on a mg-to-mg basis, and several patients have been known to have received accidental intravenous doses of strong ropivacaine with little serious ill-effects.[6,12] However, toxicity is still an important issue, and convulsions have been reported by other workers.[23–26] In only one of these cases was there any evidence of significant cardiac toxicity, which occurred after a relatively large dose was administered (225 mg).[26]

In our study, one patient experienced symptoms suggestive of central nervous system toxicity (tinnitus, vertigo and tingling around mouth and throat) after receiving 150 mg of ropivacaine. This was followed by a short period of loss of consciousness, but the cardiovascular system was at no point compromised. There were no visible seizures and she recovered quickly, but she was taken out of the study and given general anaesthesia for her caesarean section. She was considered to have received only a partial intravenous dose since she did develop a T8-S1 sensory block, so some of the dose appears to have reached the epidural space. Of note here is that blood had been seen in the epidural catheter when it was first sited, but (in accordance with common practice) the catheter had been pulled back and flushed, and had appeared to be safe to use. This is a salient reminder that epidural catheters are never truly safe, and that particular care and vigilance is necessary when a bloody tap has been observed. In addition, using epinephrine in the epidural solution might have aided in the early detection of intravenous administration.

The other patient who "collapsed" during the administration of the study solution (stopped after 14 mL) developed bradycardia, hypotension and reduced level of consciousness. This was initially feared to be the result of local anaesthetic toxicity from accidental intravenous administration, but it became clear quite quickly that actually this was a vasovagal faint, and she recovered rapidly after the administration of small doses of atropine and ephedrine. She was removed from the study, but went on to develop an excellent block after a total of 20 mL of the study solution (ropivacaine) and her caesarean section was performed under epidural anaesthesia.

In this study of 80 women undergoing caesarean section under epidural anaesthesia, six (7%) were given spinal anaesthesia and three (4%) were given general anaesthesia. This failure rate is higher than one would wish in normal clinical practice, but importantly, only two women required emergency *intraoperative* conversion to general anaesthesia for pain and discomfort. This is consistent with the results from a recent survey of UK practice, which showed that the mean rate of intraoperative conversion from epidural to general anaesthesia was 6%, with very wide inter-hospital variation.[1]

The relatively poor performance of epidural anaesthesia in this study was disappointing (supporting the widespread popularity of spinal anaesthesia for elective caesarean section) and is probably a reflection of several factors. Firstly, this study was performed in a teaching establishment where the epidurals were performed by a number of different anaesthetists of varying experience, and several of the failures appeared to be technical. Secondly, sensory block was tested with ethyl chloride spray. Although using cold sensation is a widely practised technique amongst obstetric anaesthetists in the UK,[27] it is now apparent that light touch may be a more reliable tool for assessing adequacy of the sensory block for pain-free surgery.[28]

This study was designed to test whether one new licensed drug could effectively replace the commonly used unlicensed mixture of bupivacaine and fentanyl, and the opioid was therefore omitted from the ropivacaine group. However, since the licensing of drugs frequently lags behind clinical practice, and the use of drugs "off-label" is widespread, particularly in obstetrics, licensing is perhaps not such a significant issue.[29]

In addition, pruritus does not seem to have been a significant problem in group BF, and therefore withholding fentanyl from the ropivacaine group was probably unnecessary and unhelpful. Ropivacaine is also considerably more expensive than racemic bupivacaine plus fentanyl, and the increased cost cannot be justified on the basis of our findings.

Our results confirm that plain ropivacaine 0.75% can be used as the local anaesthetic for epidural elective caesarean section. However, it showed no clinical advantage over the popular mixture of bupivacaine 0.5% + fentanyl 100 μg, and, contrary to expectation, produced a denser and more prolonged motor block.

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