Comparison of epidural anaesthesia with ropivacaine 0.5% and bupivacaine 0.5% for Caesarean section

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Purpose: To compare ropivacaine 0.5% with bupivacaine 0.5% for epidural anaesthesia for Caesarean section.

Methods: Healthy pregnant women, scheduled for elective Caesarean section were enrolled into this randomized, double-blind, parallel-group study. Epidural block was obtained with 20-30 ml of ropivacaine (group R) or bupivacaine (group B) and surgery started when anaesthesia was reached T₆. Maternal heart rate and blood pressure and fetal heart rate were assessed before the test dose and at five minute intervals until the end of surgery. At the same intervals, sensory and motor block characteristics were determined. Apgar scores and Neurologic and Adaptive Capacity Scores (NACS) were determined after delivery. Adverse events were recorded.

Results: Sixty-five patients were enrolled and data from 61 were available for analysis; 30 ropivacaine and 31 bupivacaine. Time from the end of the last injection to the start of surgery was 46 ± 13 min (mean $\pm$ SD) in gp R and 53 ± 25 min in gp B (P :NS). The median duration of analgesia varied between 1.7 and 4.2 hr in gp R and between 1.8 and 4.4 hr in gp B (P :NS). In patients who developed Bromage 4 block, it persisted longer in those in gp B (2.5 hr) than in gp R (0.9 hr) ($P < 0.05$). The quality of analgesia was satisfactory in 27/29 patients (93%) in gp R and 27/31 patients (87%) in gp B (P :NS), although supplemental iv opioid was required in ten and seven patients, respectively. The most common adverse events in the mother were hypotension (63% gp R and 61% in gp B) (NS) and nausea (30% and 58%, in group R and B, respectively) ($P = 0.05$). Apgar scores were 7 after five minutes in all neonates.

Conclusion: Ropivacaine 0.5% and bupivacaine 0.5% provided effective epidural anaesthesia for Caesarean section although supplementation with iv opioid was commonly required.

Objectif : Comparer la ropivacaine 0,5 % avec la bupivacaine 0,5 % pour une anesthésie péridurale pendant un accouchement par césarienne.

Méthode : Des femmes enceintes, en santé, devant subir une césarienne électorale, ont été recrutées pour la présente étude randomisée et en double aveugle de deux groupes parallèles. Le blocage péridural a été obtenu avec 20 - 30 ml de ropivacaine (groupe R) ou de bupivacaine (groupe B) et la chirurgie a débuté quand l'anesthésie avait atteint T₆. La fréquence cardiaque et la tension artérielle de la mère ainsi que la fréquence cardiaque du fœtus ont été enregistrées avant l'administration de la dose test et à des intervalles de cinq minutes jusqu'à la fin de la chirurgie. Pendant les mêmes intervalles, on a déterminé les caractéristiques sensitives et motrices de l'anesthésie. L'indice d'Apgar et les indices de capacité neurologique et adaptative (ICNA) ont été déterminés après la naissance. Les événements indésirables ont été enregistrés.

Résultats : Soixante-cinq patientes ont été recrutées et on a recueilli les données pour analyse chez 61 d'entre elles : 30 dans le groupe ropivacaine et 31 dans le groupe bupivacaine. La période entre la fin de la dernière injection et le début de la chirurgie a été de 46 ± 13 min (moyenne $\pm$ écart type) dans le groupe R et de 53 ± 25 min dans le groupe B (P : NS). La durée moyenne de l'analgesie varie de 1,7 à 4,2 h dans le groupe R et de 1,8 à 4,4 h dans le groupe B (P : NS). Parmi les patientes qui ont présenté un niveau 4 à l'échelle de Bromage, l'analgesie a duré plus longtemps chez les femmes du groupe B (2,5 h) que chez celles du groupe R (0,9 h) ($P < 0,05$). La qualité de l'analgesie a été satisfaisante chez 27 des 29 patientes (93 %) du groupe R et chez 27 des 31 patientes (87 %) du groupe B (P : NS), bien qu'il ait fallu ajouter des opioïdes iv pour dix et sept patientes, respectivement. Les incidents défavorables les plus fréquents chez les mères ont été l'hypotension (63 % du groupe R et 61 % du groupe B) (NS) et les nausées (30 % et 58 %, dans les groupes R et B, respectivement) ($P = 0,05$). L'indice d'Apgar a été de 7 après cinq minutes chez tous les nouveau-nés.

Conclusion : La ropivacaine 0,5 % et la bupivacaine 0,5 % fournissent une anesthésie péridurale efficace pendant la césarienne bien qu'une dose supplémentaire d'opioïdes iv soit fréquemment requise.

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ROPIVACAINE is a new long-acting amide local anaesthetic. It is structurally closely related to a chemical group of aminoamides in present clinical use, e.g. bupivacaine and mepivacaine. The latter are racemic mixtures, whereas ropivacaine is the pure (S)-enantiomer. It is available as the monohydrate of the hydrochloride salt of 1-propyl-2,6-pipecoloxylidide. Ropivacaine has pharmacodynamic and pharmacokinetic properties in animals resembling those of bupivacaine.¹⁻³ However, in animals, ropivacaine has a lower central nervous system and cardiotoxic potential than bupivacaine.⁴ In human volunteers, ropivacaine has been shown to be less prone than bupivacaine to produce mild central nervous system and cardiovascular changes after intravenous infusion.⁵

Initial clinical studies in epidural anaesthesia have indicated that pharmacodynamic and pharmacokinetic properties for ropivacaine are comparable to those seen with bupivacaine.⁶⁻⁸ The onset and duration of sensory block and the overall clinical efficacy of anaesthesia have been reported to be comparable for the two drugs. However, the frequency, degree and duration of motor block may be less with ropivacaine than with bupivacaine when used in equal concentrations. Adverse events with ropivacaine have mainly been those compatible with the sympathetic block of epidural anaesthesia (hypotension, bradycardia, nausea and vomiting). The incidence of these events appears to be similar after ropivacaine and bupivacaine.

The present study was designed to evaluate the quality and nature of epidural block achieved with ropivacaine 0.5% in patients undergoing Caesarean section and to compare it with that achieved when bupivacaine 0.5% was used.

Patients and methods

Patient enrollment

The study was randomized double-blind and with two parallel treatment groups. Four centres participated in the study. Pregnant women who gave informed consent to an institutionally approved protocol were studied. Patients were eligible for enrollment if they were ASA I-II, with full-term singleton fetuses, scheduled for elective Caesarean section with or without tubal ligation under epidural anaesthesia, ≥ 18 yr of age, ≥ 150 cm in height and ≤ 100 kg in weight. Patients were not eligible if there was a history of allergy or sensitivity to amide-type local anaesthetics, maternal diabetes, a psychiatric history which could lead to unreliability in the clinical assessment, alcohol, drug or medication abuse as judged by the investigator or a contraindication for epidural procedures.

The patients were randomized in blocks of six within each centre. Double-blindness was maintained by means of the identical appearance of the ropivacaine and bupivacaine solutions and ampoules.

Anaesthetic protocol

One litre of crystalloid solution was administered before initiation of the epidural block. The epidural catheter was placed with a 16-18G Tuohy needle in the L₂₋₃ or L₃₋₄ interspace, using the midline approach, with the patient in the sitting or lateral position. A test dose of 3 ml lidocaine 1.5% with 15 μ g epinephrine was used to assess catheter placement. Following this, 20 ml of the study drug (100 mg) was injected through the epidural catheter at a rate of 4 ml·min⁻¹. Surgery was started when analgesia was achieved at the T6 dermatome level, assessed with pin prick by a blinded research nurse using a short beveled 23G needle, and adequate surgical anaesthesia was obtained. Adequate surgical anaesthesia in this context signified no pain after using a clamp to pinch the skin within the area of incision.

If the block did not reach dermatome level T₆ or if surgical anaesthesia was not obtained within 30 min, an additional 5 ml (25 mg) of the study drug were given. If the block did not reach T₆ or if surgical anaesthesia was not obtained after a further 15 min (45 min after injection of the main dose), another 5 ml (25 mg) were given. If the block did not reach T₆ or if surgical anaesthesia was still not achieved after another 15 min (60 min after main dose), the patient was withdrawn from further efficacy assessment and received an anaesthetic regimen at the discretion of the investigator.

Assessments of sensory block were performed by the research nurse at 5, 10, 15, 20, 25, 30, 45 and 60 min after the main dose, and then every 30 min until the return of normal sensation. The onset and end of analgesia was determined bilaterally, using a short beveled 23G needle. Analgesia was recorded at dermatome levels S₃, S₁, L₅, L₃, L₁, T₁₂, T₁₀, T₈ and T₆; together with the maximal spread of analgesia (upper and lower spread).

Assessments of motor block were performed immediately after the assessments of sensory block until the return of normal motor function. The onset and end of all degrees of motor block were assessed bilaterally according to the modified Bromage scale: 1 = inability to raise extended leg (able to flex knee); 2 = inability to flex knee (able to move foot only); 3 = inability to flex ankle joint (unable to move foot or knee); and 4 = complete motor paralysis (unable to move foot, knee or toes).

Maternal heart rate and systolic and diastolic blood pressure were measured with a automated non-invasive blood pressure cuff. Values were recorded before the test dose and at five-minute intervals during surgery, and then every 30 min for up to three hours. A systolic blood pressure of < 90 mmHg or > 180 mmHg, was considered to be hypotension or hypertension, respectively. A heart rate of < 50 bpm or > 140 bpm was considered to be bradycardia or tachycardia, respectively. A systolic blood pressure < 90 mmHg was treated with 5-10 mg ephedrine *iv* and a heart rate < 50 bpm was treated with 0.6 mg atropine *iv*.

Pain on incision was recorded as being present or absent and, if present, its intensity was assessed using a ten point visual analogue scale. At any time after delivery, the patient could be given 50 µg fentanyl *iv* if she experienced pain or discomfort. The quality of anaesthesia (i.e. quality of analgesia and abdominal wall muscle relaxation) was assessed by the investigator and surgeon after the end of the operation as: 1) satisfactory; 2) satisfactory until a specified time; or 3) unsatisfactory.

Fetal and neonatal assessments

Fetal heart rate was monitored continuously and recorded at the same intervals as maternal heart rate until the patient's abdomen was prepared for surgery. Evaluation of the newborn was done by the research nurse by means of Apgar Scores at one and five minutes after birth, and by Neurologic and Adaptive Capacity Scores (NACS) at 2 and 24 hr after birth.⁹ Neurologic and Adaptive Capacity Score has been developed as a screening test to detect central nervous system depression caused by drugs and also to differentiate these effects from those found after birth trauma and perinatal asphyxia. The NACS is based on 20 criteria. These criteria assess five general areas: 1) adaptive capacity; 2) passive tone; 3) active tone; 4) primary reflexes; 5) alertness, crying and motor activity. Each criterion is given a score of 0, 1 or 2, based on whether the response to testing is absent or grossly abnormal (score 0), mediocre or abnormal (score 1) or normal (score 2). The maximum possible score is 40. A total NACS score of 35-40 is considered to indicate neurologically vigorous neonates.⁹

Adverse Events

Both the mother and the baby were assessed for adverse events. An adverse event was defined as any unfavourable, unintended event, temporally associated with administration of the study drug, whether or not considered to be drug related. If an adverse event occurred more than 14 days after the patient's most

TABLE I Patient demographics

	<i>Ropivacaine</i> (<i>n</i> = 30)	<i>Bupivacaine</i> (<i>n</i> = 31)
Age (mean ± SD)	31 ± 6 yrs	32 ± 4 yrs
Height (mean ± SD)	161 ± 6 cm	161 ± 6 cm
Weight (mean ± SD)	76 ± 11 kg	76 ± 9 kg
ASA Risk Group I / II	23 / 7	26 / 5

TABLE II Most common adverse events in mother before delivery, by treatment group.

<i>Event</i>	<i>Ropivacaine</i> (<i>n</i> = 30)	<i>Bupivacaine</i> (<i>n</i> = 31)
Hypotension	19	19
Lightheadedness	3	2
Paraesthesia	4	2
Bradycardia	1	1
Nausea	5	10
Vomiting	1	3
Shoulder pain	1	1
Shivering	2	1

TABLE III Most common adverse events in fetuses and neonates, by treatment group.

<i>Event</i>	<i>Ropivacaine</i>	<i>Bupivacaine</i>
<i>Fetal</i>		
Bradycardia		1
Tachycardia		1
<i>Neonatal</i>		
Apnoea		1
Vomiting	1	
Congenital malformation	3	2
Tachypnoea	1	3
Tachycardia	1	
Respiratory distress	1	1
Grunting	1	

recent use of the study drug and there existed no apparent evidence to support a causal connection or relationship, the event was not considered to constitute an adverse event. A serious adverse event was one which constituted a definite hazard or handicap to the mother or child. Adverse events were recorded during anaesthesia and surgery, in the recovery room, daily during hospitalization, and at a follow-up two to three weeks after surgery.

Approaches to analysis

Patients for whom the study was terminated as technical failures were withdrawn from the study. Technical

FIGURE Frequency of various degrees of motor block (percentage of patients).

failure was defined as: a total failure to achieve epidural block considered by the investigator to be due to an incorrectly placed injection. Patients who were considered technical failures and received the study drug were not included in the statistical analysis with the exception of the safety analysis. Technical failures and other patients not valid for the "per protocol" analysis were replaced by additional patients randomized to one of the treatment groups. Patients with inadequate spread of sensory block (not achieving T_6) or inadequate surgical anaesthesia one hour after administration of the study drug were withdrawn from further efficacy assessments. Patients judged to be in need of additional analgesics/anaesthetics before the end of surgery were withdrawn from further efficacy assessments.

Two approaches to the statistical analysis were used: a "per protocol" (PP) analysis and an "all patients treated" (APT) analysis. The APT analysis was used for efficacy analysis and a patient was excluded from the APT analysis in the event of: technical failure or if the patient did not receive any study drug. A patient was excluded from the PP analysis in the event of: violation of inclusion/exclusion criteria; major protocol violation which could influence the validity of data; patients withdrawn from the study for a reason which was not related to the study drug but which would result in considerable loss of data; or technical failure.

Statistical methods

Sample size determination:

The sample size for the study was calculated with the aim of showing a difference between treatments in duration of motor block, with a mean difference of at least one hour. Based on the published literature, the standard deviation of Bromage 1 motor block was

assumed to be approximately 1.1 hr. With 30 patients in each group and using a significance level of 0.05, the power of the study was 93%. The calculation was made using the t test, based on the assumptions of normally distributed data, and equal variances.

ANALYSIS OF RESULTS

Proportions were analyzed by the use of the chi-square test, or, if the expected frequency in any cell was less than 5, Fisher's exact test. All tests were two-tailed and performed at a significance level of 0.05.

Missing values are assumed to be missing at random. They have not been included in the analysis and have been taken into consideration only by the reduced sample sizes.

Results

Patient description

Sixty-five patients were enrolled into the study. Two patients (one in each group) were technical failures and two patients in the ropivacaine group did not receive the study drug. The study was prematurely discontinued in six other patients, three in each group and these patients were not included in the per protocol analysis. In four cases, two per group, the block was inadequate for surgery, in one (ropivacaine) there was a protocol deviation and in another (bupivacaine) additional analgesia was required to complete the surgery. Thirty patients received ropivacaine and 31 received bupivacaine (APT analysis). The groups were well matched regarding demographic data (Table I).

Anaesthetic and block characteristics

The mean volume of study drug administered was 22 ml ropivacaine and 21.3 ml bupivacaine ($P:NS$). Twenty-one patients (21/30, 70%) of the ropivacaine patients received 20 ml study drug, six (20%) received 25 ml and three (10%) received 30 ml compared with 26 (26/31, 84%) who received 20 ml, two (6.3%) who received 25 ml and three (9.7%) who received 30 ml, respectively for bupivacaine ($P:NS$). Ten patients in the ropivacaine group received supplemental opioid intraoperatively compared with seven in the bupivacaine group ($P:NS$). The quality of anaesthesia was satisfactory in 93% of patients in the ropivacaine group and 87% in the bupivacaine group ($P:NS$).

The median onset time for sensory block, within dermatomal levels relevant for surgery (T_6-S_3), varied between 7.5 and 25 min in the ropivacaine group and 5 and 17.5 min in the bupivacaine group. The time between the end of administration of the main dose and the start of surgery was 46 ± 13 min (mean $\pm$ SD) for

ropivacaine and 53 ± 25 min for bupivacaine (P :NS). The median duration of sensory block within dermatomal levels relevant for surgery varied between 1.7 and 4.2 hr for ropivacaine and 1.8 and 4.4 hr for bupivacaine. The median maximum upper segmental spread was T₅ in the ropivacaine group and T₄ in the bupivacaine group and the median maximum lower segmental spread was S3 in both groups (P :NS). The median onset time for motor block by degree with ropivacaine were 15, 30, 56 and 60 min for degree 1, 2, 3, and 4 respectively and for bupivacaine were 12.5, 20, 25 and 30 min, respectively (P :NS). The frequency of various degrees of motor block is presented in Figure 1. The median duration times for motor block degrees 1,2,3, and 4 with ropivacaine were 2.1, 1.5, 1.2 and 0.9 hr. For bupivacaine, the median duration times for motor block degrees 1,2,3, and 4 were 2.4, 1.9, 1.8, and 2.5 hr, respectively. In those patients who developed a Bromage 4 motor block (five in the ropivacaine group and four in the bupivacaine group), the block persisted longer in patients who had received bupivacaine ($P < 0.05$). There were no other significant findings with respect to block characteristics.

Adverse effects

The most common adverse effects is reported in Tables II and III. Hypotension occurred in 19 patients in each group. Five patients who received ropivacaine experienced nausea before delivery and one vomited compared with ten and three, respectively in the bupivacaine group (P :NS). After delivery, four patients in the ropivacaine group experienced nausea and three vomited compared with nine and five, respectively in the bupivacaine group (P :NS). Overall, 30% of the patients who received ropivacaine experienced nausea compared with 58% of those who received bupivacaine. ($P = 0.05$) There were no other differences between the groups with respect to the nature and incidence of adverse effects.

Neonatal assessments

Twenty-eight of 30 (93%) of the neonates in the ropivacaine group and 30/31 (97%) of those in the bupivacaine group had an Apgar score of 7 at one minute; all had a score of 7 at five minutes (P :NS). In one patient (bupivacaine), persistent fetal bradycardia developed 15 min after injection of the main dose. Urgent Caesarean section was carried out under general anaesthesia with a good outcome but the patient was removed from drug efficacy assessment as it was not possible to assess the block characteristics fully.

In the *all patients treated* (APT) analysis a NACS 35 at two hours was registered in 23/30 (77%) neonates in the ropivacaine group and 16/30 (53%)

in the bupivacaine group (P :NS). However, in the *per protocol* (PP) analysis, a NACS 35 was seen in 22/27 (81%) of patients in the ropivacaine group and 14/27 (52%) of the bupivacaine group. ($P = 0.043$) At 24 hr, only one neonate in the ropivacaine group and three in the bupivacaine group had scores of <35 (P :NS).

Discussion

In this study, both ropivacaine 0.5% and bupivacaine 0.5% produced effective and well-tolerated epidural anaesthesia in patients undergoing Caesarean section although there was a need for supplementation of the block with intravenous opioid in about a third of the patients in each group. The magnitude and duration of sensory and motor block did not differ between the groups with one exception. The duration of Bromage 4 motor block, in those patients who developed it, was shorter in patients who received ropivacaine. This finding was likely influenced by the relatively small number of patients (nine in total) with this characteristic and the influence of outliers on small group numbers.

Several studies have demonstrated a longer duration of sensory block with bupivacaine than with ropivacaine.^{10,11} Our study, however, confirmed the results of other workers; in equal doses and concentrations, the profile of sensory block with time is the same for ropivacaine and bupivacaine.¹²⁻¹⁴ Our data also showed that the both Bromage score and time to onset of motor block were similar in patients who received ropivacaine and bupivacaine. Others have also found no difference in onset time and a shorter duration of motor block^{10-12,14} although one study found that motor block was not only of shorter duration in patients who received ropivacaine, it was also later in onset.¹³ Others have reported that ropivacaine produced a less intense motor block motor.^{11,14}

The quality of anaesthesia was considered by the patients to be satisfactory in 93% of patients who had ropivacaine and 87% of those who had bupivacaine. This is comparable to the finding of Griffin and Reynolds who concluded that extradural block was inadequate for surgery in 10% of patients in each treatment group.¹² Previous studies of elective Caesarean section under extradural anaesthesia using plain bupivacaine 0.5% also had a high incidence of inadequate block with 20-30% of patients requiring supplemental analgesia with nitrous oxide or opioids (an option not available in our study protocol).^{15,16} Although this is an unacceptably high incidence of inadequate anaesthesia, the addition of epidural opioids to ropivacaine may reduce this problem, as it does with bupivacaine.

Maternal adverse events were evenly distributed across treatment groups, the most common adverse

events in the mothers were hypotension and nausea. Our incidence of maternal adverse effects is similar to that reported by others. These events are expected in association with epidural administration of local anaesthetics. Neonatal adverse events were few and evenly distributed across treatment groups; none were attributed specifically to the study drug.

Analgesics and anaesthetics administered for Caesarean section may have neonatal effects persisting after birth; general anaesthesia is more depressant to the neonate than is regional anaesthesia. A transient decrease in NACS at two hours after birth was also seen in the newborns of mothers who had received bupivacaine in one subgroup analysis (PP) but not the other (APT). If this finding is real, it would indicate a difference between the treatments on neurobehaviour performance during the first hours of life after Caesarean section. However, our results are not consistent with others reporting no adverse effects on NACS by bupivacaine given for epidural analgesia during labour¹⁷ and no difference in the incidence of a NACS < 35 in neonates born to mothers receiving either ropivacaine or bupivacaine for epidural anaesthesia.¹² The clinical importance of our finding is uncertain. All of the neonates had high scores at 24 hr and none had persistent sequelae.

In summary, we found that ropivacaine 0.5% and bupivacaine 0.5% produced a similar duration of sensory analgesia and both agents produced equally satisfactory block for Caesarean section. A more rapid recovery from motor block with ropivacaine 0.5 % may be advantageous but it has not been a consistent finding in all studies. Maternal adverse effects were similar in their incidence and likely more technique- than drug-related. The incidence of inadequate block requiring supplementation, with both bupivacaine 0.5% and ropivacaine 0.5%, is concerning; it is likely that ropivacaine would achieve an improved quality of block at higher administered concentrations or if supplemented with epidural opioids as has been demonstrated with bupivacaine.

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