The Comparison Of Intrathecal Isobaric Ropivacaine And Isobaric Ropivacaine-Clonidine For Caesarean Delivery
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Citation

Abstract
Aim: We investigated the effects of intrathecal isobaric 0.5% ropivacaine and isobaric 0.5% ropivacaine-clonidine combination in women undergoing caesarean deliveries.

Methods: Twenty-five parturients received 17.5 mg ropivacaine (group R) and twenty five parturients received 15 mg ropivacaine and 30 µg clonidine (group RC) for spinal anaesthesia. Sensory and motor block properties; haemodynamics, postoperative analgesia, foetal outcomes and side effects were evaluated. Unpaired and paired-t-tests and chi-square and Mann-Whitney-U tests were used where appropriate (p<0.05).

Results: Intrathecal ropivacaine and ropivacaine-clonidine provided effective sensory anaesthesia and motor block. S2 dermatome regression time was longer in ropivacaine-clonidine combination. First minute APGAR was lower in group RC (mean 8.8±0.7) than group R (mean 9.3±1.0). Umbilical venous pH and fifth minute APGAR scores were similar between the groups. Postoperative analgesia was prolonged by clonidine. Although intraoperative ephedrine requirements (mg) were higher in ropivacaine-clonidine group, the number of patients requiring ephedrine and the number of hypotension episodes were similar. Dry mouth was observed more with clonidine.

Conclusion: We concluded that, intrathecal 17.5 mg 0.5% isobaric ropivacaine provides efficient and safe anaesthesia for caesarean section delivery. The addition of 30 µg clonidine to 15 mg 0.5% isobaric ropivacaine results in longer complete and effective analgesia with similar block properties. In both groups, hypotension was easily treated with ephedrine and did not affect maternal and neonatal outcome.

INTRODUCTION
Ropivacaine has pharmacodynamic and pharmacokinetic properties resembling those of bupivacaine in animals and humans but with less motor block, central nervous system toxicity and cardiotoxicity. Intrathecal ropivacaine studies are present in obstetric and nonobstetric patients. But, the optimal safe and effective dose, baricity and the effects of adjuvants to ropivacaine for obstetrical anaesthesia are still to be determined.

Clonidine produces spinal analgesia by interacting with the alpha-2 adrenergic receptors. The synergy between clonidine and local anaesthetics is well known. Intrathecal clonidine was combined with ropivacaine in only D’Kock et al's study for knee arthroscopy. And it is known to improve analgesia in labour either alone or in combination with other agents. However, There is only one study combining clonidine with a local anesthetic (bupivacaine) in caesarean sections.

Although systemic toxicity of local anaesthetics is not a problem for intrathecal administration; block characteristics such as onset and duration of analgesia, the quality of muscle relaxation, haemodynamic stability, and side effects are important for caesarean section (C/S) anaesthesia. Therefore, the minimal effective dose should be used in parturients to provide safety of the mother and the foetus. In a previous study, we found that 15mg isobaric ropivacaine with morphine provided sufficient anesthesia for C/S. Wong et al's study revealed a minimum dose of 18.75 or 22.5 mg for Chinese women. ED value in Khaw et al 's study was 16.7 mg.
This study was designed to determine the effects of adding clonidine to ropivacaine to reduce the dose of ropivacaine in women undergoing caesarean section operations.

**METHODS**

**PATIENTS**

After institutional ethical committee approval and written informed consent, 50 ASA physical status I or II elective parturients who had single babies at term were included into the study. The parturients with maternal cardiac disease, maternal haematological disease, diabetes, eclampsia, bleeding or coagulation test abnormalities, foetal distress, known foetal anomalies were excluded from the study. Patients were premedicated with oral sodium citrate (30 ml) 30 minutes before the spinal block. Hydroxyetilstarch solution 6% (500 ml) was given preoperatively as preload.

**PILOT STUDY**

Before the study, a pilot study was performed to determine the dose of ropivacaine that will be used in the study, taking into account the previous study doses. In the pilot study, plain 15 mg ropivacaine resulted in insufficient anaesthesia in five C/S patients. General anaesthesia was required for all patients because of patient discomfort and pain. That is why the dose of the plain ropivacaine group was increased to 17.5 mg for the study. We hypothesized that clonidine would potentiate the effects of ropivacaine, therefore the dose of ropivacaine was kept at 15 mg in the clonidine-ropivacaine group.

**PREPARATION OF STUDY DRUGS**

Using a computer-generated randomisation table, patients were randomised to one of two groups to receive the study solution containing either 0.5% 17.5 mg of isobaric ropivacaine (Naropin; Astra-Zeneca) [Group R (n=25)], or 0.5% 15 mg of isobaric ropivacaine plus 30 µg clonidine (Duraclon, Roxane) [Group RC (n=25)]. The study solution was prepared at the time of caesarean section by a supervisor who was aware of the content of the study solutions but not involved in data collection. The investigators as well as the patients were blinded to the contents of the study solutions.

**MONITORING AND STUDY PERIOD**

After entering the operation theatre, patients were monitored (Poet II, Criticare Systems Inc. USA) for observing heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO₂) and respiration rate (RR). Lactated Ringer’s solution was infused in doses of 10 ml kg⁻¹ hour⁻¹ during surgery. Spinal anaesthesia was performed using a 25-Gauge Quincke needle in the sitting position at L₃₋₄ or L₄₋₅ interspaces in all groups. The study solutions (3.7 ml) were administered within 30 seconds (approximately 0.12 ml-1 second⁻¹) with the opening of the needle facing cephalad, and the position of the needle was confirmed by aspiration and reinjection of 0.2-0.5 ml cerebrospinal fluid flow before and at the end of administration of the study solution. Immediately after, the patients were gently placed supine with left uterine displacement and a pillow was placed under the head. For the assessment of foetal heart rates, a foetal heart rate monitor was used until delivery.

After the spinal block, HR, RR, SpO₂ and MAP were measured every minute until delivery and then every 2 minutes and were recorded one minute after spinal block, at surgical incision and then every 10 minutes. Hypotension was defined as 20% decrease from baseline MAP (Baseline MAP was calculated from three measurements in the ward preoperatively) and if episodes of hypotension lasts during 1 minute, hypotension was treated with 10 mg incremental boluses of IV ephedrine. Total ephedrine requirements, number and lasting of episodes were recorded. Patients breathed spontaneously, and supplementary oxygen was given through a facemask during the operation. Urine output was also monitored.

The level and duration of sensory anaesthesia, defined as the loss of sharp sensation was evaluated by using the pinprick test at midclavicular level, every minute until reaching T₅ dermatome and then every 10 minutes during surgery. The following variables were recorded: time to initial onset of analgesia; time to maximum cephalad spread of analgesia;
highest level of analgesia; time until sensory block has reached T5 dermatome; time to two segment regression of analgesic level from T5 dermatome and regression of analgesic level to S₂ dermatome. Anaesthesia was considered adequate for surgery if pain sensation was lost at the T5 level.

The quality of anaesthesia (judged by anaesthetists), the quality of muscle relaxation (judged by surgeon) and degree of intraoperative comfort (judged by patient) were recorded as excellent, good, fair or poor. Intraoperative pain and the feeling of discomfort were evaluated by the patient and recorded by an observer unaware of patient data using visual analog scale.

Time to motor block was assessed every minute with Bromage Scale (0= no motor block to 3= complete motor block of both lower limbs) until complete motor block was achieved and every 15 minutes until the return of normal motor function. The time to complete motor block, complete recovery and the motor block score when sensory level reached T5 were recorded.

The time to first feeling of pain (complete analgesia) and time to first request of analgesics (effective analgesia) were recorded.

In the intraoperative period, dry mouth, nausea, vomiting, pruritus, shivering and requirement of sedation or general anaesthesia (if needed) were recorded. Nausea and vomiting were treated with 10 mg i.v. metoclopramide. Diphenhydramine 20 mg i.v. was administered for pruritus.

Maternal sedation scores were evaluated and recorded intra and postoperatively until the block had worn off using a grading score from 0= no sedation to 3= severe sedation with difficulty to arouse. The patients remained in a semi-recumbent position in the post-anaesthesia care unit, until full recovery of spinal block.

The time from uterine incision to delivery was recorded. After delivery, umbilical blood samples were obtained for umbilical venous blood gases and APGAR scores at 1st and 5th minutes were evaluated and recorded.

During 48 hours postoperatively, side effects including pruritus, headache, backache, respiratory depression, nausea-vomiting, and urinary retention were recorded. On the fifth day, patients were called from their homes to ask for side effects. Satisfaction of patients on perioperative period was assessed by a four point scale (poor to excellent).

**POWER AND STATISTICAL ANALYSIS**

Data from DeKock et al study [9], including standard deviations of time to sensory block to S₂ with ropivacaine and ropivacaine-clonidine were used for power analysis. To detect 30-min difference in mean duration in time to regression to S₂ segment between the groups (two sided of 5% and of 20%), a group size of 21 or 22 was necessary.

SPSS 10.0 version was used for statistics. Unpaired and paired-t-test were used for quantitative nominal data (mean±SD) whereas categorical data were compared using χ² and Mann-Whitney-U test where appropriate. p<0.05 was considered significant.

**RESULTS**

Spinal block was successfully performed in all cases. No haemorrhage or paraesthesia was observed in both groups. None of the patients needed supplementary analgesics or sedation for surgery. All patients reported excellent intraoperative analgesia. Excellent muscle relaxation was reported in 98% of patients in the group R and 100% in the ropivacaine-clonidine group by the surgeon.

Patient demographics were similar (p>0.05)

**Figure 2**

Table 2: Demographic and surgical data

<table>
<thead>
<tr>
<th></th>
<th>Group R</th>
<th>Group RC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>161.2±4.3</td>
<td>162.3±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2±16.1</td>
<td>77.3±14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>30.4±4.6</td>
<td>28.5±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Number of Pregnancy</td>
<td>2.2±0.9</td>
<td>2.3±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of C/S</td>
<td>0.6±0.7</td>
<td>0.6±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Week of gestation</td>
<td>39.0±1.0</td>
<td>38.9±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>22.9±7.7</td>
<td>22.0±6.5</td>
<td>NS</td>
</tr>
<tr>
<td>Delivery time (min)</td>
<td>1.4±0.9</td>
<td>1.4±0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant

Sensory, motor and sympathetic block properties are presented in Table 3. There was no difference between the
groups in onset time, time to reach T5 sensory level, in the maximum sensory cephalad spread level, time to maximum cephalad spread and the motor block score when the sensory level reached T5. While the time to regression of two dermatomes was similar, time for the block to recede to S2 dermatome was longer in group RC than and R (p<0.05). The time to reach complete motor block and time to complete recovery from motor block were found similar between group RC and R (p>0.05). The number of hypotension episodes and duration of episodes were similar in both groups (p>0.05). Total ephedrine requirements were higher in group RC than group R (p<0.05). Ephedrine was used in 19 patients of group R (76%), and 23 patients in group RC (92%) (p>0.05).

The values of mean arterial pressures are presented in figure 1. In group RC, MAP decreased significantly (p<0.05) one minute after the spinal block when compared to group R. All other measurements of MAP were similar in both groups (p>0.05).

Postoperative analgesia characteristics are presented in Table 4. The time to first feeling of pain and the time to request of first analgesic were longer in group RC than R (p<0.05).
The Comparison Of Intrathecal Isobaric Ropivacaine And Isobaric Ropivacaine-Clonidine For Caesarean Delivery

Table 4: Postoperative analgesia

<table>
<thead>
<tr>
<th>Group R (17.5mg)</th>
<th>Group RC (15mg+30μg)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=25)</td>
<td>(n=25)</td>
<td></td>
</tr>
<tr>
<td>Time to first feeling of pain (min)</td>
<td>112.4±20.6</td>
<td>140.2±22.2</td>
</tr>
<tr>
<td>Time to first request (hr)</td>
<td>3.5±1.2</td>
<td>6.8±2.2</td>
</tr>
</tbody>
</table>

APGAR scores and umbilical venous pH values are presented in table 5. All of the umbilical venous blood pH values were in normal range. APGAR scores at the first minute after delivery were lower in group RC than group R (p<0.05) but all APGAR scores in first minute were not lower than 6. Fifth minute APGAR scores were similar in both groups and all APGAR scores in fifth minute were no lower than 9 (p>0.05). Umbilical venous blood pH values were similar in both groups (p>0.05).

Table 5: Umbilical venous pH and APGAR scores

<table>
<thead>
<tr>
<th>Group E (n=25)</th>
<th>Group RC (n=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical venous pH</td>
<td>7.36±0.04</td>
<td>7.34±0.07</td>
</tr>
<tr>
<td>APGAR (1st min)</td>
<td>9.3±1.0 (7-10)</td>
<td>8.8±0.7 (8-10)</td>
</tr>
<tr>
<td>APGAR (5th min)</td>
<td>9.9±0.2 (9-10)</td>
<td>10.0±0.0 (10)</td>
</tr>
</tbody>
</table>

Umbilical venous pH values are expressed as mean±SD. The APGAR values in parenthesis represent the minimum and maximum scores of the groups.

During the intraoperative period, dry mouth incidence was significantly higher in group RC than group R (the number of patients were 18 and 3 respectively) (p<0.05). The number of patients with nausea-vomiting and requirements of metoclopramide were similar (p>0.05). Pruritus was observed in 1 patient in group R and 1 patient in group RC (p>0.05). Postdural puncture headache was observed similarly in both groups and was managed simply by administration of fluids and analgesics. Respiratory depression, shivering, backache were not observed in any patient during all perioperative period Sedation (>1) was not observed in any patient in both groups.

DISCUSSION

Previous studies with intrathecal ropivacaine suggest adding an opioid to ropivacaine to improve the quality of analgesia [10,12]. Despite apparently adequate spread of sensory anaesthesia with ropivacaine, the quality of intraoperative analgesia varies and intraoperative pain exists [10,12]. They also considered that spinal ropivacaine was significantly less potent than spinal bupivacaine as like previous other studies [5,6,7,8]. In Mc Namee and co-workers' study [10] 18.75 mg and 25 mg ropivacaine were used for major orthopaedic surgery and intraoperative analgesia was judged to be excellent. But, in 19 patients of 51 in 7.5 mg/ml group and 25 patients of 53 in 10 mg/ml group sensory anaesthesia rose proximal to the T4 dermatome and even reached to C4 dermatome. In these patients they did not detect motor weakness, respiratory distress or cardiovascular compromise. In one patient they encountered inadequate anaesthesia. Mc Namee et al study [10] suggests that despite ropivacaine produces significant high cephalad spread, its analgesia quality may not correlate with the level of sensory analgesia. To achieve sufficient analgesia with ropivacaine for caesarean section operation or major abdominal surgery the dose of ropivacaine should be higher than bupivacaine. Additionally, using higher dose of ropivacaine to obtain sufficient analgesia may lead to adverse local anaesthetic
side effects especially in obstetric patients. For this reason we aimed to reduce ropivacaine dose using an adjuvant, clonidine. Pregnant patients are at more risk of spinal opioid side effects [9]. As a spinal adjuvant, clonidine is being extensively evaluated as an alternative to spinal opioids for the control of pain. It is free of some opioid-related side effects such as respiratory depression, nausea and pruritus [9]. There are a few studies with clonidine used as an adjuvant for obstetrical anaesthesia [17,18,19,20,21-23]. This study is the first intrathecal ropivacaine-clonidine combination for caesarean deliveries.

We used the lowest probable dose determined from Chung et al study [9] which used 18 mg hyperbaric ropivacaine and Mc Namee et al study [10] which used 18.75 mg isobaric ropivacaine and from other previous isobaric ropivacaine studies conducted by Wahedi et al (15 mg), Malinovsky et al. (15 mg), van Klee et al. (15 mg) and Gautier et al (14 mg) for lower extremity or urological operations [18,19,20,21]. It is known that spinal injections in full term pregnant patients produce higher than expected anaesthesia levels, and isobaric local anaethetics result in unpredictable block [21,22]. At body temperature, 0.5% ropivacaine solution is considered slightly hypobaric (density at 37°C: 0.9988) [22] that may result in a higher cephalad spread, when administered in the sitting position [21,22]. To avoid unpredictable cephalad spread, we used doses lower than Chung et al.’s study and the same as in other isobaric studies.

Intrathecal clonidine (30µg) has been combined previously with local anaesthetic (LA) or/and opioids for labour analgesia [17,18,19,20]. Sia et al [19] stated that when intrathecal 15 and 30 µg clonidine was added to sufentanil plus bupivacaine for labour analgesia, 30µg clonidine was associated with a higher incidence of hypotension and sedation but there was no clinically evident adverse effect. In Gautier et al study [20] 30 µg clonidine was not detected in foetal circulation at delivery. Both studies were intended for labour. Our study was conducted in caesarean operations that require more profound anaesthesia for surgery. Our selected dose of 30µg is a considered as a low or mini dose by D’Angelo [17,20]. Our results show that, the combination of 30µ clonidine provided similar onset and cephalad spread but longer sensory analgesia when compared with a higher dose of plain ropivacaine. Similarly, De Kock et al [1] stated that; clonidine combination prolonged sensory analgesia time in a dose-dependent manner, but adding clonidine to ropivacaine did not change analgesia onset time and cephalad spread.

In our study we observed complete motor block in all patients. Our results indicate that intrathecal ropivacaine causes profound motor block with rapid onset, and prolongs duration similar to the previous studies [9,10,11]. In our previous study [12] we had observed, spinal ropivacaine–morphine combination provided shorter duration but similar intensity of motor block when compared with bupivacaine-morphine combination in parturients. Malinovsky concluded that the intensity and duration of motor block of intrathecal ropivacaine were similar with bupivacaine. Mc Namee et al [11] concluded that duration and intensity of motor block were related to the dose of ropivacaine. It was reported that intrathecal clonidine might prolong the duration and increase the depth of motor block [15,17,22]. De Kock et al [1] observed that degree and duration of motor block correlated with increasing clonidine doses. We did not use different clonidine doses but the addition of clonidine to 15 mg ropivacaine produced similar duration and depth of the motor block with 17.5 mg plain ropivacaine in our study.

Prolonging the effective postoperative analgesia obtained with spinal anaesthesia after caesarean delivery may be an advantage. Intrathecal alpha-2 agonists produce potent antinociceptive effects, alter spinal neurotransmitter release and are effective in acute nociceptive and chronic neuropathic pain [14,15,16,17,18,19,20]. Previous studies [19,17,18,19,20,22] have demonstrated that the addition of intrathecal clonidine considerably prolongs the duration of analgesia with bupivacaine or an opioid. In our study, the complete and effective analgesia times in the ropivacaine-clonidine group were prolonged. Yanagidate et al [22] found that preoperative oral clonidine reduces the PCA morphine requirement after caesarean delivery without compromising the condition of the foetus or newborn. Nader et al [1] pointed that preoperative administration of clonidine decreased catecholamine release in the central nervous system and suppresses plasma and cerebrospinal fluid concentrations of TNF-alpha that regulates adrenergic responses in the brain. In our study, pre-emptive analgesia contributed to prolonged analgesia during postoperative period in clonidine-ropivacaine group. Clonidine may produce pre-emptive analgesia when used preoperatively.

Side effects of clonidine are related with the route of administration and dose. Larger clonidine doses are associated with hypotension, bradycardia, and transient...
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In previous hyperbaric ropivacaine studies, various incidences of backache localised in the lumbosacral area have been reported [15,12,16]. It is interesting that in isobaric studies including ours back pain was not encountered [18]. This aspect warrants further investigation. The incidence of postdural puncture headache was 8% (4/50) in our patients. Our PDPH incidence is similar with previously reported incidences with 25 G Quincke needle (8.7%) in obstetric patients [13].

In conclusion, intrathecal 17.5 mg 0.5% isobaric ropivacaine provides efficient and safe anaesthesia for caesarean section delivery. The addition of 30 µg clonidine to 15 mg 0.5% isobaric ropivacaine results in longer complete and effective analgesia with similar block properties and helped to reduce the effective dose of ropivacaine and improved intraoperative muscle relaxation when compared plain ropivacaine for caesarean delivery. Clonidine combination with ropivacaine did not affect maternal and neonatal outcome. Further studies are needed on the effects of clonidine-ropivacaine combinations for obstetric anaesthesia.

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References

sedation via intrathecal or epidural route [10,13]. It was stated that, 150 µg intrathecal clonidine produces notable side effects including hypotension, sedation and dry mouth, although no delayed hypotension or bradycardia in women undergoing caesarean section operations [15]. Sedation is one of the most consistent effects mediated by central alpha-2 receptors. Sedation was also dose dependent and more pronounced after 450 µg intrathecal clonidine [18]. Similar to DeKock et al study [18] we did not observe increase in sedation with 30 µg clonidine. We did not also observe maternal and foetal bradycardia.

Central mediated hypotensive effects of clonidine have been well recognised. The mechanism for these actions may involve inhibition of sympathetic outflow and the potentiation of parasympathetic nervous activity [11,13]. Decreases in blood pressure and incidence of treatment with vasoconstrictors are only slightly increased by adding 75-225 µg clonidine to 15mg bupivacaine. In contrast, adding 150 µg clonidine to a smaller dose of bupivacaine (5 mg) caused a greater decrease in blood pressure [19,11].

Intrathecal 50-150 µg clonidine was used as a sole agent during first stage of labour or 150 µg after caesarean section operations without remarkable side effects [18,13]. Although clonidine does not produce an additional hypotensive effect when combined with local anaesthetics, there is a potential for exacerbating haemodynamic depression from the combination of intrathecal clonidine with opioids [11]. In previous labour studies, clonidine added to local anaesthetic in doses between 15-150 µg was reported to cause mild to moderate hypotension without any effect on neonatal outcomes [18,17,19,20]. In our study, moderate hypotension requiring ephedrine use was observed in both groups after the spinal block. Although ephedrine requirement was higher in the clonidine group, it was not clinically significant. Maternal or foetal sequel of hypotension was not observed in both groups.

Intrathecal clonidine used alone or in combination with local anaesthetics (in doses of 15-150 µg) does not affect foetal outcome [16,17,18,19,20]. In our study, there were no adverse effects on newborn infants. The lack of difference in umbilical blood pH values suggests that any effect is not caused by change in placental or foetal cardiac function. After delivery there was no sedation in infants judged by APGAR scores. There was no report from postnatal nursing staff of any delay in the time to first request for feeding by the infants.
28. Tuominen M, Kalso E, Rosenberg PH. Effects of posture on the spread of spinal anaesthesia with isobaric 0.75% or 0.5% bupivacaine. Br J Anaesth 1982; 54:313-8.
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