Comparison of ropivacaine (0.2%) with or without clonidine 1 μg/kg for epidural labor analgesia: A randomized controlled study

Indira Kumari, Kapil Sharma¹, Vikram Bedi², Madhan Mohan², Hemraj Tungaria², Manish Kumar Modi²
Departments of Anesthesiology and Critical Care, ¹Anesthesiology and Pain Management and ²Anesthesiology, RNT Medical College, Udaipur, Rajasthan, India

Background and Aims: The aim is to determine the effect of addition of clonidine to ropivacaine for epidural labor analgesia with regard to onset of analgesia, duration of analgesia, neonatal outcome, and quality of analgesia.

Material and Methods: A total of 60 term parturients of the American Society of Anesthesiologists Grade I and II with uncomplicated pregnancy, vertex presentation, posted for on-demand epidural labor analgesia after informed consent were divided in two groups. Group R (n = 30) patients received 10 ml solution comprising 0.2% ropivacaine. Group RC (n = 30) patients received a total of 10 ml of 0.2% ropivacaine and clonidine 1 μg/kg. Characteristics of the block, onset and duration of analgesia, and total analgesic requirements were noted. Pain and overall satisfaction scores were assessed with a 10-point visual analog scale. Mode of delivery and neonatal APGAR scores were recorded.

Results: Maternal demographic characteristics were comparable between the groups. Addition of clonidine to ropivacaine shortened the onset and prolonged the duration of analgesia with decrease in ropivacaine requirement in Group RC. There was a significant difference between the two groups regarding visual analog score and quality of analgesia, which was better in Group RC. There were no significant differences between the two groups regarding motor block, hemodynamic parameters, and neonatal outcomes.

Conclusion: We conclude that clonidine in low doses is a useful adjuvant to local anesthetics for epidural labor analgesia and a good alternative to opioids.

Keywords: Clonidine, labor analgesia, ropivacaine

Introduction

One of the most severe pains experienced by a woman is that of the childbirth. The pains of labor result in a maternal stress response which is neither beneficial to the fetus nor the mother.[1] Providing analgesia for labor has always been a challenge, more so because of the myths and controversies surrounding labor.

Of all the available pain relief techniques, epidural analgesia is the gold standard technique for labor analgesia. A reduction in the concentration of local anesthetics and the addition of adjuvants has been advocated to improve results and minimize risks in epidural labor analgesia. This allows the patient to be ambulatory with preservation of motor function and subjective somatic sensation in the lower limbs resulting in better maternal satisfaction.[2] It is achieved with very low concentrations of the local anesthetics and adjuvants such as opioids and alpha-2
agonists,\textsuperscript{[3,4]} thereby minimizing the adverse effect of both the local anesthetics as well as the adjuvants. Several studies\textsuperscript{[5,6]} have shown that addition of clonidine improves the quality of anesthesia, reduces the dose requirement of the anesthetic agent, and provide better hemodynamic stability with no adverse effects on fetal or maternal outcome.

However, more studies are required for strong recommendation for routine use of clonidine in labor analgesia\textsuperscript{[7]} and to further confirm that epidural clonidine does not have any adverse impact on neonatal well-being.\textsuperscript{[6]} Hence, we planned this study to compare the effect of addition of clonidine (1 µg/kg) to ropivacaine (0.2%) for epidural labor analgesia.

**Material and Methods**

The present study was carried out in a tertiary care teaching hospital. Institutional ethical committee clearance was obtained for the study and written informed consent was obtained from each patient before enrolment in the study.

The primary outcome measure in the present study was a prolongation of the duration of analgesia (visual analog scale [VAS] ≤3) in the clonidine group as compared to control group. In earlier study done by Landau \textit{et al.},\textsuperscript{[5]} the duration of analgesia in clonidine group was increased to 132 ± 48 min as compare to 91 ± 44 min in control group. Based on this for our study to have a power of 80% and Type 1 error of <0.05, 27 patients would be require in each group. We have taken thirty patients in each group to compensate for drop out. A total of 60 full-term parturients belonging to the American Society of Anesthesiologists Grade II with uncomplicated pregnancy in vertex presentation were include in trial while those with hypersensitivity to study drugs, bleeding disorders, local or systemic sepsis, spinal column disorders, blood/cerebrospinal fluid (CSF) in the epidural catheter during procedure, and with history of drug abuse were excluded from the study. Parturients were divided into two groups of thirty each. Group R patients receiving 10 ml of 0.2% Ropivacaine (Ropin™, Neon Laboratories, India Ltd.) epidurally. The solution was prepared by drawing 3 ml of 0.5% ropivacaine in a 10 ml syringe and adding 7 ml of saline to obtain 10 ml of 0.2% ropivacaine.

Group RC patients received 10 ml of 0.2% Ropivacaine (Ropin, Neon Laboratories, India Ltd) and Clonidine (Clonion™, Neon Laboratories, India, Ltd.) 1 µg/kg epidurally. The solution was prepared by adding 1 µg/kg of a 100 mcg/ml solution of clonidine to 3 ml of 0.5% ropivacaine and injection normal saline q.s. 10 ml.

The parturients were assigned to either group randomly using the list of computer-generated numbers in sealed envelopes. The solutions were prepared by a separate anesthetist and the anesthetist who administered the drug and recorded response was blinded to group allocation.

After a thorough preanesthetic examination, participating parturients in active labor having at least one contraction every 5 min were shifted to the labor room, an 18-gauge intravenous cannula was inserted into the dorsum of nondominant hand and 500 ml of RL started. All the parturients were monitored by standard pulse oximetry, NIBP, three leads electrocardiogram.

Parturients in both groups were placed in the left lateral position and under strict aseptic precautions, a local infiltration of 2% lignocaine was done into the intervertebral space. Epidural space was identified at L3-4 or L4-5 level using a loss of resistance technique to normal saline with an 18-gauge Tuohy needle and an 18-gauge multiorifice catheter was threaded through the cranially directed tip of the epidural needle to a depth of 5 cm into the epidural space. No local anesthetic was injected through the epidural needle before catheter placement. After negative aspiration for CSF and blood, a 3-ml test dose of the study medication was administered through the catheter as per group allocation. The presence of clinical sign of an intravascular injection was sought for the following 2–3 min. If there were no sign of an intravascular injection, the catheter was secured and the women were placed in supine position with left uterine displacement.

Five minutes after the test dose, if there were no clinical signs of subarachnoid injection (as evidenced by the patient’s ability to move her legs and the absence of hypotension), additional 7 ml of the study solution was administered in increments of 2–3 ml. The adequacy of analgesia was assessed 5 min after the last dose of local anesthetic had been administered and every 2 min thereafter for 15 min, by asking the patient whether she felt pain at the peak of a contraction. She was also asked to rate her level of pain on the visual analog scale.

Anesthesia was considered to be adequate if the patient reported acceptable pain relief even if the pain score was not zero. If she said that analgesia was not adequate, an additional 10 ml of study medication was administered, and the analgesia was reassessed in the same manner 5 min later. Inadequate pain relief despite the second dose was considered as failure and the patient was excluded from the study. The patient was assessed for the presence of motor block in lower extremities using a modified Bromage score every 2 min for 15 min and then every 15 min.
Vital parameters of the parturients, pulse and BP were recorded every 5 min for the first 30 min, then every 30 min until the study was completed. Pain and motor block scores, block height (level), balance, and ability to stand was assessed at 30 min interval until the study was completed. Fetal heart rate (FHR) was monitored throughout the study using a transducer and any evidence of FHR deceleration was recorded. The following estimations were done:

1. Quality of analgesia – quality of analgesia throughout labor was assessed by the following scoring system (Celleno and Capogna 1988)[8]
   0: failure, 1: incomplete, 2: good, 3: excellent, and 4: not possible to evaluate as needed delivery by cesarean section
2. Block level – the spread of sensory block were assessed by pinprick from the unanesthetised to the anesthetised zones and also perceived temperature difference to spirit swab.

Motor block assessment:

Breen modified Bromage score, 1993[9]
- Grade 1: Complete block (unable to move feet or knees)
- Grade 2: Almost complete block (able to move feet only)
- Grade 3: Partial block (just able to move knees)
- Grade 4: Detectable weakness of hip flexion (between scores 3 and 5)
- Grade 5: No detectable weakness of hip flexion while supine (Full flexion of knees)
- Grade 6: Able to perform partial knee bend while standing.

3. VAS

VAS was assessed on a scale of 0 to 10, with 0 as no pain and 10 as maximum possible pain, every 15 min for 3 h and, whenever the patient demanded analgesia. Rescue analgesia in the form of local anesthetic as per the institutional protocol was administered when VAS was >3 and the time to rescue analgesia was noted.

4. Parturients’ acceptance;

Degree of pain relief or quality of analgesia.
- Grade 3: Excellent – with the uterine contraction, patient has no sensation of pain
- Grade 2: Good – the patient was aware of uterine contraction and experienced dull backache
- Grade 1: Incomplete or Fair – the patient experienced some pain or the relief was on one side only even with advancing labor with increased intensity of uterine contraction
- Grade 0: Failure or poor – there was no pain relief.

Side effects including nausea, vomiting, hypotension, hypersensitive reaction, shivering, fever, drowsiness, pruritus, respiratory depression, retention of urine, weakness in limbs, and accidental dural puncture were assessed at 0, 5, 15, 30.60, and then every hour, until complete cervical dilation and delivery.

5. Neonatal assessment was done by assessing the APGAR score at 1 and 5 min.

Statistical analysis
Data were analyzed using Epi Info six and Microsoft Excel version 10(Microsoft Corporation,Washington). Parametric data were compared using two-sided, two sample t-tests and nonparametric data were compared using the Mann–Whitney U-test. Discrete data were compared using Chi-square test. Significance level was taken at \( P < 0.05 \).

Results

Data were obtained for all sixty parturients with no dropouts. Patients in the two groups were comparable in terms of demographic and obstetric parameters [Table 1]. The mean time of onset of analgesia was significantly lower in Group RC compared to Group R [Table 2]. The VAS at 5, 10, and 15 min was significantly lower in RC when compared to Group R [Figure 1]. Patient in Group RC also reported a significantly longer duration of analgesia when compared to Group R [Table 3]. The requirement of total dose of ropivacaine was significantly higher (\( p<0.001 \)) in Group R (55.50 ± 14.2 mg) than in Group RC (40.00 ± 12.0 mg).

A significantly lesser numbers of top-up doses were required in Group RC when compared to Group R. There were no significant complications in any patient at either group.

No significant difference was observed among the two groups in terms of motor power and patient satisfaction. There were no episodes of clinically or statistically significant hypotension or bradycardia in the group that received epidural clonidine.

Discussion

Administration of epidural local anesthetic continuously is the most widely used method of providing labor analgesia in modern day practice. The holy grail of labor analgesia is to achieve complete pain relief with minimal motor blockade and neonatal adverse effect. To do so, the research is targeted at use of local anesthetic agents and adjuvants.
Ropivacaine has been used in neuraxial, peridural, and subarachnoid anesthesia. It has a profile similar to bupivacaine, but with less neuro- and cardio-toxic effect.\cite{10,11} Clonidine is an alpha-2 agonist that produces analgesia through nonopioid mechanism.\cite{12,13} Although a slightly larger dose of ropivacaine is required to achieve analgesia, addition of opioids and clonidine to ropivacaine provides the opportunity to use more diluted solutions for better analgesia, and reduces the risk of systemic toxicity and incidence of motor block.\cite{5,14,15}

The present study aimed to determine whether addition of 1 µg/kg clonidine to epidural administered ropivacaine resulted in improvement in labor analgesia when compared to ropivacaine alone.

We observed that the patients who received ropivacaine with clonidine had a faster onset of analgesia, longer pain-free duration, and required lesser number of epidural top ups, when compared to those who were given ropivacaine alone.

Similar results have been reported by Ahirwar et al.\cite{16} and Landau et al.\cite{5} A decrease in onset of analgesia by addition of clonidine to ropivacaine can be explained by various mechanisms including the effect on descending noradrenergic tract in the spinal cord that plays an important role in pain modulation by a nonopioid mechanism.\cite{17} Noradrenergic ganglions in pons and medulla cannot be activated by opioid or noxious stimulus that causes norepinephrine secretion at dorsal horn of spinal cord.\cite{18,19} A reduction in the onset time of analgesia depends on definition of onset time of each study. While Syal et al.\cite{7} used a decrease in NRS level by two levels; Landau et al.\cite{5} defined onset as maximum targeted pain relief. We have defined the onset time as satisfactory pain relief reported by parturients, which is the most reliable indicator of ascertaining pain relief.

A prolongation of analgesia and reduction in total dose required for painless vaginal delivery by addition of clonidine to ropivacaine is supported by several other authors including Landau et al.\cite{5} and Topcu et al.\cite{20} who conducted a prospective, randomized blind study to compare analgesic effectiveness of fentanyl and clonidine supplementation to ropivacaine for patient-controlled epidural analgesia (PCEA) during labor. Seventy-two healthy pregnant women in labor were randomly allocated to three groups equally as Group R; 0.1% ropivacaine, Group RF; 0.1% ropivacaine and 1 µg/ml fentanyl, and Group RC; 0.1% ropivacaine and 0.75 µg/ml clonidine solutions. PCEA was applied to the patient with pump programmed as 5 ml bolus dose, 10 min locking time (no basal infusion, no 1–4 h limit), and 10 ml loading dose (from the study solution). Maternal hemodynamics, quality of analgesia (visual analog scale), motor block, sedation, and maternal and fetal side effects were evaluated.

### Table 1: Demographic data

| Data                  | Group R (n=30) | Group RC (n=30) | P    |
|-----------------------|---------------|-----------------|------|
| Age (years)           | 24.6±3.2      | 26.2±3.1        | 0.055|
| Weight (kg)           | 59.0±6.0      | 60.5±4.2        | 0.256|
| Height (cm)           | 157.8±3.1     | 156.9±3.2       | 0.277|

SD=Standard deviation

### Table 2: Onset of analgesia

| Time of onset | Group R | Group RC | P |
|---------------|---------|----------|---|
| 5-8           | 9       | 4        |   |
| 9-12          | 9       | 21       |   |
| 13-16         | 21      | 5        |   |
| Mean time of onset | 13.5±1.9 | 10.6±1.8 | <0.001 |

### Table 3: Block characteristics

| Data                                      | Group R | Group RC | P    |
|-------------------------------------------|---------|----------|------|
| Mean VAS at 0 min                         | 9.8±0.5 | 9.7±0.6  | 0.61 |
| Mean VAS after bolus (5 min)              | 7.2±1.3 | 6.07±0.94| <0.001|
| Mean VAS after bolus (10 min)             | 4.5±0.9 | 1.9±1.8  | <0.001|
| Mean VAS after bolus (15 min)             | 1.7±1.1 | 0.6±1.0  | <0.001|
| Height of sensory block                   | T10     | T10      | -    |
| Injection delivery interval               | 192.9±39.4 | 191.8±37.3 | 0.912|
| Mean duration of analgesia of bolus dose (min) | 70.9±11.5 | 108.0±14.1 | <0.001|
| Mean first top-up time                    | 72.3±15.7 | 109.5±17.7 | <0.001|
| Mean subsequent second top-up time        | 55.9±10.2 | 58.2±7.9  | 0.260|

VAS=Visual analog score

Ropivacaine has been used in neuraxial, peridural, and subarachnoid anesthesia. It has a profile similar to bupivacaine, but with less neuro- and cardio-toxic effect.\cite{10,11} Clonidine is an alpha-2 agonist that produces analgesia through nonopioid mechanism.\cite{12,13} Although a slightly larger dose of ropivacaine is required to achieve analgesia, addition of opioids and clonidine to ropivacaine provides the opportunity to use more diluted solutions for better analgesia, and reduces the risk of systemic toxicity and incidence of motor block.\cite{5,14,15}
They found that analgesic dosage was significantly decreased in Group RC when compared with Group R ($P < 0.05$) and in fentanyl supplemented Group RF, when compared with Group R ($P < 0.05$) and Group RC ($P < 0.01$). They concluded that fentanyl or clonidine addition to ropivacaine in PCEA for labor decrease local anesthetic consumption.

There was no significant difference in the motor block, mode of delivery and neonatal outcome in the two groups.

A major limitation of our study is that we have not used continuous epidural infusion for LA or PCEA in either group, the inclusion of these two techniques may have reduced the LA requirements, shortened the time of onset and enhanced the duration of analgesia in both groups.

**Conclusion**

In conclusion that the addition of clonidine 1 µg/kg to epidurally administered ropivacaine 0.2% improves the onset of analgesia, prolongs its duration, and is very well accepted by the parturients. The addition of this dose of clonidine does not result in any significant increase in the incidence of undesirable motor blockade, cesarean section/instrumental vaginal delivery, or neonatal depression when compared to ropivacaine.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Shnider SM, Abboud TK, Artal R, Henriksen EH, Stefani SJ, Levinson G. Maternal catecholamines decrease during labor after lumbar epidural anesthesia. Am J Obstet Gynecol 1983;147:13-5.
2. Nageotte MP, Larson D, Rumney PJ, Sidhu M, Hollenbach K. Epidural analgesia compared with combined spinal-epidural analgesia during labor in nulliparous women. N Engl J Med 1997;337:1715-9.
3. Motsch J, Gräber E, Ludwig K. Addition of clonidine enhances postoperative analgesia from epidural morphine: A double-blind study. Anesthesiology 1990;73:1067-73.
4. Förster JG, Rosenberg PH. Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. Br J Anaesth 2004;93:670-7.
5. Landau R, Schiffer E, Morales M, Savoldelli G, Kern C. The dose-sparing effect of clonidine added to ropivacaine for labor epidural analgesia. Anesth Analg 2002;95:728-34.
6. Nakamura G, Ganem EM, Módolo NS, Rugolo LM, Castiglia YM. Labor analgesia with ropivacaine added to clonidine: A randomized clinical trial. Sao Paulo Med J 2008;126:102-6.
7. Syal K, Dogra R, Ohri A, Chauhan G, Goel A. Epidural labour analgesia using Ropivacaine and Clonidine. J Anaesth Clin Pharmaco 2011;27:87-90.
8. Celleno D, Capogna G. Epidural fentanyl plus bupivacaine 0.125 per cent for labour: Analgesic effects. Can J Anaesth 1988;35:375-8.
9. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg 1993;77:919-24.
10. Pitkanen M, Feldman HS, Arthur GR, Covino BG. Chronotropic and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Reg Anesth 1992;17:183-92.
11. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield E, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563-9.
12. Tremlett MR, Kelly PJ, Parkins J, Hughes D, Redfern N. Low-dose clonidine infusion during labour. Br J Anaesth 1999;83:257-61.
13. Paech MJ, Pavy TJ, Orlikowski CE, Evans SF. Patient-controlled epidural analgesia in labor: The addition of clonidine to bupivacaine-fentanyl. Reg Anesth Pain Med 2000;25:34-40.
14. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. Systemic toxicity of ropivacaine during ovine pregnancy. Anesthesiology 1991;75:137-41.
15. Turner G, Scott DA. A comparison of epidural ropivacaine infusion alone and with three different concentration of fentanyl for 72 hours of postoperative analgesia following major abdominal surgery. Reg Anesth 1998;23:A39.
16. Ahirwar A, Prakash R, Kushwaha BB, Gaurav A, Chaudhary AK, Verma R, et al. Patient Controlled Epidural Labour Analgesia (PCEA): A comparison between ropivacaine, ropivacaine-fentanyl and ropivacaine-clonidine. J Clin Diagn Res 2014;8:GC09-13.
17. Sullivan AE, Dashwood MR, Dickenson AH. Alpha 2-adrenoceptor modulation of nociception in rat spinal cord: Location, effects and interactions with morphine. Eur J Pharmacol 1987;138:169-77.
18. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996;85:655-74.
19. Asano T, Dohi S, Ohta S, Shimonaka H, Iida H. Antinociception by epidural and systemic alpha(2)-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. Anesth Analg 2000;90:400-7.
20. Topcu I, Erinciler T, Tekin S, Karaer O, Isik R, Sakarya M. The comparison of efficiency of ropivacaine and addition of fentanyl or clonidine in patient controlled epidural analgesia for labour. Internet J Anesthesiol 2006;11:1-7.