ORIGINAL RESEARCH

Addition of neostigmine on dose requirement of ropivacaine 0.1% in labouring patients receiving lumbar epidural analgesia: Hemodynamic changes

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ABSTRACT
Epidurally administered Ropivacaine is effective in providing analgesia during labour. It is recommended to administer 10-20 ml bolus of Ropivacaine 0.2% with intermittent 20-30 mg top up injections or a continuous epidural infusion of Ropivacaine 0.2% (6-10 ml/hr.) for labour analgesia. The analgesic efficacy of Ropivacaine is almost similar to or slightly less than bupivacaine. The difference in incidences of operative deliveries when Ropivacaine was compared with bupivacaine was also not found significant. Patients were randomized into two groups using computer generated random numbers: **GROUP A:** Received 0.1% Ropivacaine with fentanyl 2µg/ml in 10 ml total volume. **GROUP B:** Received 0.1% Ropivacaine with fentanyl 2µg/ml and neostigmine 500µg in 10 ml total volume. Baseline hemodynamic parameters likematernal heart rate, oxygen saturation, ECG, non-invasive blood pressure, wererecorded. The mean maternal heart rate at 45min interval in group A was 88.56 (± SD 3.20) and in group B was 92.32 (±SD 5.00), which was statistically significant (p value 0.003).The mean maternal heart rate at 180min interval was 87.32 (±SD 2.66) in group A and 90.16 (±SD 5.54) in group B, which was statistically significant (p value 0.025).

Key words: Neostigmine, labouring patients, hemodynamic changes

INTRODUCTION

It is a potential space within the bony cavity of the spinal canal and outside the dural sac. Anteriorly bounded by the bodies of vertebrae, intervertebral discs and posterior longitudinal ligament. Posteriorly it is bounded by the anterior surface of the vertebral laminae and ligarnentumflava. Superiorly bounded by the fusion of dura and periosteum at the foramen magnum, inferiorly by the sacrococcygeal ligament at sacral hiatus, laterally by the pedicles of vertebrae and intervertebral foramina.The shape of the epidural space in cross section is nearly circular in the cervical and thoracic regions, but becomes triangular as we reach lumbar region. The depth of the epidural space is greatest in the midline in the lumbar region where it is said to be 5-6 mm in adult male, hence midline approach is recommended for entering the lumbar epidural space.[1]

The process of labour occurs in three stages. The first stage-starts from the onset of regular uterine contractions with progressive cervical dilatation to the time of fullcervical dilatation. The second stage-extends between full dilatation of the cervix and the delivery of infant. The third stage-from delivery of the infant to the time of expulsion of the placenta. Labour pain is unique because of its progressive nature; it increases in severity, frequency and duration as it progresses. The intensity of pain is so severe that as per the McGill pain questionnaire, it occupies the upper part of the pain scale between that of cancer pain and amputation of a digit.[2]

Ropivacaine, a new long acting amide local anaesthetic was synthesised by Ekenstam in 1957 and belongs to pipecoloxylidides group as that of bupivacaine and Mepivacaine.It was introduced into clinical practice in 1996 and was the first local anaesthetic to be presented as pure S-enantiomer.

Ropivacaine is used as local anaesthetic for infiltration, nerve block, and epidural and intrathecal anaesthesia.[3]

Neostigmine was first synthesized by Aeschlimann and Reinert in 1931and was patented by Aeschliman in 1933. Neostigmine is made by reacting 3-dimethylaminophenol with *N*-dimethylcarbamoyl chloride, which forms a dimethylcarbamate. Next, this product is alkylated using dimethyl sulfate, which forms neostigmine.[4]

Epidurally administered Ropivacaine is effective in providing analgesia during labour. It is recommended to administer 10-20 ml bolus of Ropivacaine 0.2% with intermittent 20-30 mg top up injections or a continuous epidural infusion of Ropivacaine 0.2% (6-10 ml/hr.) for labour analgesia. The analgesic efficacy of Ropivacaine is almost similar to or slightly less than bupivacaine. The difference in incidences of operative deliveries when Ropivacaine was compared with bupivacaine was also not found significant.[5]

The addition of opioids like fentanyl 2 µg/ml to Ropivacaine 0.1% solution administered at 10 ml/hr. significantly reduces local anaesthetic concentration.Also, the adjuvants like clonidine significantly increase the duration of action of Ropivacaine.[6]

METHODOLOGY

SOURCE OF DATA: The study was conducted in 50 Primiparous patients in active phase of labour in the labour ward of Department of Obstetrics and Gynecology.

STUDY DESIGN: Prospective, randomized, double blinded, controlled study.

SAMPLE SIZE: 50.

INCLUSION CRITERIA

1. ASA II, Consenting primigravida in labour, gestational age ≥ 36 weeks.
2. Age 18-35 years, singleton pregnancy with vertex presentation.

EXCLUSION CRITERIA

1. Allergy to anyof the study drugs.
2. Significant coagulopathy.
3. Patients with history of significant disorders (Pregnancy induced hypertension, diabetes mellitus, obstetric haemorrhage, other cardiovascular, respiratory, central nervous system or renal system disorders).
4. **OTHER CONTRAINDICATIONS:** Localized sepsis, raised ICP etc.

METHODS OF COLLECTION OF DATA

Patients were explained about the procedure and informed/written consent was obtained.

- Thorough pre anaesthetic evaluation was performed.
- Routine investigations obtained.
- Foetal status, labour status (frequency and duration of labour pain and cervical dilatation) assessed and noted both clinically and with Cardiotocography (CTG).
- Patients were randomized into two groups using computer generated random numbers:
- **GROUP A:** received 0.1% Ropivacaine with fentanyl 2µg/mlin 10 ml total volume.
- **GROUP B:** received 0.1% Ropivacaine with fentanyl 2µg/mland neostigmine 500µg in 10 ml total volume.
- Baseline hemodynamic parameters likematernal heart rate, oxygen saturation, ECG, non-invasive blood pressure, wererecorded.
- Under strict aseptic precautions epidural space identified with patient in left lateral position by midline approach using 18 G Tuohy's needle in L_{3-4} or L_4-L_5 interspace with loss of resistance to saline technique and catheter is threaded cephalad 3 to 4 cms into epidural space. After negative aspiration for blood and CSF, a test dose of 3ml of lignocaine 2% with 1:2, 00, 000 adrenaline was administered through the catheter.
- Ten ml of study drugof either 0.1% Ropivacaine with fentanyl 2µg/mlor 0.1% Ropivacaine with fentanyl 2µg/ml and Neostigmine 500µg was administered as per group allotment.
- Analgesia maintained by top up of 5 ml solution of 0.1% Ropivacaine with fentanyl 2µg/ml with NRS≥4, not earlier than 15 min of previous dose.
- Patients who experienced inadequate analgesia (NRS≥4) during the process were supplemented with additional 5 ml solution at least 15min later.

RESULTS

Table 1: Comparison of heart rate in the study subjects among the two groups

Comparison of heart rate in the study subjectsamong the two groups			
Intervals	**Group A (n=25)**	**Group B (n=25)**	**P value**
	Mean ± SD	**Mean ± SD**	
0 min	88.96 ± 5.80	89.52 ± 5.75	0.733
5 min	88.16 ± 4.28	89.60 ± 5.13	0.287
15 min	87.68 ± 5.07	90.20 ± 4.90	0.08
30 min	87.36 ± 2.66	92.72 ± 5.12	0
45 min	88.56 ±3.20	92.32 ±5.00	0.003
60 min	88.48 ± 3.51	90.36 ± 5.02	0.131
90 min	88.00 ± 3.92	89.40 ± 3.76	0.204

120 min	88.00 ± 2.81	88.92 ± 5.10	0.433
180 min	87.32 ± 2.66	90.16 ± 5.54	0.025

The mean maternal heart rate at 45min interval in group A was 88.56 (± SD 3.20) and in group B was 92.32 (±SD 5.00), which was statistically significant (p value 0.003).

The mean maternal heart rate at 180min interval was 87.32 (±SD 2.66) in group A and 90.16 (±SD 5.54) in group B, which was statistically significant (p value 0.025).

Table 2: Comparison of systolic BP in the study subjects among the two groups

Comparison of systolic BP in the study subjectsamong the two groups			
Intervals	**Group A (n=25)**	**Group B (n=25)**	**P value**
	Mean ±SD	**Mean ±SD**	
0 min	123.04 ±6.56	126.80 ±5.29	0.030
5 min	113.20 ±3.32	125.84 ±4.79	0.000
15 min	118.72 ±8.18	122.64 ±5.91	0.058
30 min	109.92 ±6.04	117.92 ±5.02	0.000
45 min	112.88 ±6.93	114.96 ±5.00	0.230
60 min	121.12 ±5.26	120.64 ±6.73	0.780
90 min	120.64 ±5.99	122 ±5.45	0.405
120 min	122.96 ±6.48	124.40 ±5.20	0.391
180 min	124.00 ±6.30	125.44 ±5.82	0.405

There was no significant fall in maternal systolic BPin both the groups recorded at different intervals.

Table 3:Comparison of diastolic BP in the study subjects among the two groups

Comparison of diastolic BP in the study subjectsamong the two groups			
Intervals	**Group A (n=25)**	**Group B (n=25)**	**P value**
	Mean ±SD	**Mean ±SD**	
0 min	78.56 ±4.06	78.00 ±3.46	0.602
5 min	77.60 ±3.46	77.28 ±3.16	0.734
15 min	76.00 ±4.16	75.04 ±3.92	0.405
30 min	69.92 ±15.04	73.76 ±4.10	0.224
45 min	74.16 ±4	72 ±3.87	0.058
60 min	76.48 ±3.33	75.04 ±4.44	0.201
90 min	76.88 ±3.56	78.00 ±2.77	0.221
120 min	77.76 ±4.29	78.72 ±2.37	0.333
180 min	77.92 ±3.58	79.20 ±3.61	0.214

The mean diastolic BP recorded at various intervals in both the groups were statistically insignificant.

DISCUSSION

BAWDANE *et al.*: In their prospective, randomized, double-blind study, randomly allocated 60 women in labour to receive either bupivacaine 0.1% with fentanyl 2 μg/mL (B-F group), or Ropivacaine 0.1% with fentanyl 2 μg/mL (R-F group). Bromage scale, loss of cold sensation to ether swab in midclavicular line, visual analog scale were used to test for motor block, sensory block and pain, respectively. Hemodynamic parameters, onset of analgesia, dose requirement of drug to produce analgesia, duration of labour, and incidence of side effects were recorded. They found that both drugs were similar with respect to hemodynamic stability, onset of analgesia, quality of analgesia, sensory blockade, neonatal outcome, requirement of drugs, duration of labourand incidence of side effects. Three parturient in bupivacaine (B-F) group had a motor block of Bromage 1 and were delivered using forceps, none of the parturient in Ropivacaine (R-F) group had any motor block, and all had spontaneous vaginal delivery, but this difference was not statistically significant (P = 0.081). They concluded that Bupivacaine and Ropivacaine provide equivalent analgesia in low (0.1%) concentration.[7]

FERNANDEZ-GUISASOLA *et al.*:Compared the analgesic efficacy and the degree of motor block achieved with epidural infusion of 0.0625% bupivacaine (Group B) versus 0.1% Ropivacaine (Group R), both with 0.0002% fentanyl (2 μg/mL) in labouring patients. A prospective, double-blinded study was performed in 98 ASA physical status I-II primiparous patients who were divided randomly into two groups to receive either bupivacaine or Ropivacaine after catheter location had been tested with an initial bolus of Lidocaine and fentanyl. The infusion rate was 15 mL/hr. in every case. When pain

was perceived, 5mL boluses of the assigned epidural analgesic were administered every 10 min until analgesia was achieved. They recorded pain intensity, level of sensory block, degree of motor block, hemodynamic variablesand secondary effects, mode of delivery, neonatal outcomeand patient satisfaction. They found that there were no statistically significant differences in any of the factors analysed. Highly effective analgesia was achieved in both the groups with a small incidence of motor block. They concluded that bupivacaine may be more potent than ropivacaine[7].

ROELANTS *et al*.:Studied the efficacy of concurrent epidural administration of clonidine and neostigmine in the first stage of labour as well as the effect of both drugs on subsequent local anaesthetic consumption throughout the course of labour. 100 healthy parturient with ASA physical status of I or II with gestational age >36 weeks and who requested epidural analgesia during labour were enrolled in the study. At the beginning of labour, parturient were randomly allocated to one of five groups to receive one of the following after a test dose: 150 µg epidural clonidine, 750 µg neostigmine, or 75 µg clonidine combined with 250, 500, or 750 µg neostigmine. A pain score (visual analog scale, 0-100) was recorded before administration and at regular intervals until request for a supplemental injection. Subsequent analgesia was provided by continuous epidural infusion of Ropivacaine. They found that Clonidine 150 µg, neostigmine 750 µg, and 75 µg clonidine plus 250 µg neostigmine produced ineffective and short-lasting effects. Clonidine 75 µg plus 500 µg neostigmine and 75 µg clonidine plus 750 µg neostigmine presented comparable durations of 90±32 and 108±38 min (mean±SD), respectivelyand final analgesic efficacies, with 72.2% and 84%, respectively, of the parturient reporting a visual analog scale score of less than 30 out of 100 after 30 min. Ropivacaine use was significantly reduced in all clonidine groups (average, 9.5 mg/hr.) in comparison with neostigmine alone (17±3 mg/hr.). No adverse effects were observed for 75 µg clonidine combined with any dose of neostigmine while maternal sedation (20%) and hypotension (33%) occurred with 150 µg clonidine alone. They concluded that Epidural clonidine 75 µg, with 750 µg neostigmine is an effective combination to initiate selective labour analgesia without adverse effects and that Clonidine use further reduces local anaesthetic consumption throughout the course of labour.[9]

CHAURASIA, *et al*.: In a randomized control trial compared epidural butorphanol with neostigmine and epidural Sufentanil with neostigmine for labour analgesia. The ASA Grade I and II, healthy parturient with gestational age >36 weeks(admitted in the labour room), with established first stage of labour (3-5 cm cervical dilatation, 80% cervical effacement) and receiving oxytocin infusion during the course of labour were enrolled in the study. The parturient were randomly allocated to one of the three study groups - Group A (n = 30) received butorphanol 1 mg and neostigmine 7 µg/kg, Group B (n = 30) received Sufentanil 10 µg and neostigmine 7 µg/kg, Group C (n = 30) received neostigmine 7 µg/kg and 0.9% normal saline. Maternal hemodynamic parameters and foetal heart rate (FHR) were continuously monitored. The level of sensory and motor block, and visual analog scale (VAS) pain score were recorded at designated time points. In addition, the total duration of analgesia, duration of labour, mode of delivery, and any maternal or foetal adverse effects were also recorded.They found that there was a statistically significant longer effect of analgesic drug in Group B with respect to Group A and C ($P < 0.001$); however, the parturient in Group C had minimum duration of analgesia. Epidural neostigmine combined with Sufentanil produces effective analgesia in early labour (VAS <30min within 10min in 63.3% of parturient and within 15 min in 83.3% parturient) with average duration of 111.67 ± 24.51 min without motor block or other side effect in mother and foetus. No significant effect was observed in the duration of labour and mode of delivery between the two groups, and none of the patients in any group had any maternal or foetal side effects. They concluded that epidural combination of Sufentanil with neostigmine provided better pain relief in terms of the total duration of analgesia and the reduction in VAS pain scores at various time points in the initial 30 min of epidural administration of drugs during the first stage of labour in parturient when compared to the epidural combination of butorphanol with neostigmine.[10]

CONCLUSION

- The mean maternal heart rate at 45min interval in group A was 88.56 (± SD 3.20) and in group B was 92.32 (±SD 5.00), which was statistically significant (p value 0.003).
- The mean maternal heart rate at 180min interval was 87.32 (±SD 2.66) in group A and 90.16 (±SD 5.54) in group B, which was statistically significant (p value 0.025).

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