Comparison of Epidural Butorphanol with Neostigmine and Epidural Sufentanil with Neostigmine for First Stage of Labor Analgesia: A Randomized Controlled Trial

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Abstract

Background: Epidural administration of neostigmine appears to be safe in the obstetric population. Recently, few studies have concluded 10 μg sufentanil to be an effective adjuvant with epidural neostigmine in providing labor analgesia. However, no study has evaluated the analgesic effect of epidural butorphanol with neostigmine for the same. Materials and Methods: The parturients 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 fetal 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 labor, mode of delivery, and any maternal or fetal adverse effects were also recorded. Statistical Analysis Used: A one-way analysis of variance (ANOVA) with post hoc Tukey’s test was used to compare mean value among the three groups for age, height, weight, gestational age, and cervical dilatation. Repeated measure ANOVA was used to compare mean difference among the time points and also the trend among the various time points for hemodynamic parameters, VAS pain score, and FHR. For inter-group comparison among the groups, post hoc Tukey test was used. Results: 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 labor (VAS <30 within 10 min 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 fetus. No significant effect was observed in the duration of labor and mode of delivery in-between the two groups, and none of the patients in any group had any maternal or fetal side effects. Conclusion: 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 labor in parturient when compared to the epidural combination of butorphanol with neostigmine.

Keywords: Butorphanol-adverse effects, epidural analgesia-adverse effects, first labor stage, neostigmine-adverse effects, pain measurement, sufentanil-adverse effects

INTRODUCTION

The ideal labor analgesia technique significantly decreases the pain of labor while allowing the parturient to actively participate in birthing experience. In addition, it should have minimal effect on the fetus or on the progress of labor. New labor analgesia techniques approach these goals.[1-4]

Neostigmine is a parasympathomimetic agent that has been recently investigated for use as an adjunct analgesic agent in the perioperative and peripartum period. While intrathecal administration is limited by a high incidence of nausea and vomiting in this patient population, the epidural route appears more promising and requires further investigation.[5,6] Epidural
administration of neostigmine appears to be safe in the obstetric population, with no reported adverse effects in the mother or fetus. Neuraxial adjuvant drugs are used to improve analgesia and to decrease complications associated with a high dose of a single drug.

Parenteral opioids can be administered with ease at a very low cost with high efficacy as labor analgesia. Some recent studies have tried to establish the effects of epidural opioids alone or epidural opioids in combination with neostigmine for labor analgesia. Recently, few studies have studied the effect of sufentanil with epidural neostigmine in providing labor analgesia.[7-9] The dose of sufentanil used with epidural neostigmine 500 μg in the aforementioned studies is 10 μg.

Butorphanol, a new synthetic opioid, has emerged as a promising agent in terms of efficacy and a better safety profile. Butorphanol has also been found to be safe both via parenteral[10] and epidural route for providing labor analgesia.[11] It has also been established that 0.25% bupivacaine when combined with 1 or 2 mg butorphanol provides optimal analgesia.[12]

However, on literature search, it was observed that no study has evaluated the analgesic effect of epidural butorphanol with neostigmine during the first stage of labor, and this combination has also not been compared with the more commonly studied combination, i.e., epidural sufentanil with neostigmine. The aim of the present study was to compare the analgesic effect of epidural butorphanol (1 mg) with epidural neostigmine (7 μg/kg) and epidural sufentanil (10 μg) with epidural neostigmine (7 μg/kg), during the first stage of labor. And their impact on labor, mode of delivery (cesarean section, instrumental vaginal delivery, and spontaneous) or any maternal and fetal adverse event were also recorded.

**Materials and Methods**

The study was undertaken following approval from the Institutional Ethical Committee-Human. Written informed consent was taken from all the participants. Duration of the study was 18 months.

**Study design**

This was a prospective, randomized, double-blind study.

**Selection criteria**

The American Society of Anesthesiologists Grade I and II, healthy parturient with gestational age >36 weeks (admitted in the labor room), with established first stage of labor (3–5 cm cervical dilatation, 80% cervical effacement) and had been receiving oxytocin infusion during the course of labor were enrolled in the study.

**Exclusion criteria**

Parturient was excluded from the study if multiple pregnancy, preterm labor, nonvertex presentation, previous cesarean or myomectomy, and any complications such as hypertensive disorder and renal failure. Patients were also excluded from the study if they had received any analgesia before epidural.

A total of 102 patients were enrolled initially, out of them 12 were excluded due to several reasons such as inability to facilitate epidural catheter insertion on time, patients who had already received intravenous (IV) analgesics or sudden progress of labor, etc. A computer-generated random number table was formed by allotting an equal number of patients to each group and finally, a total of ninety parturients were included and randomized. The consultant in-charge enrolled the participants and assigned them to the intervention whereas the investigator, patient, and the outcome assessor remained blinded to the patient group and the intervention. Baseline vitals were recorded. During the epidural block, continuous electrocardiogram, pulse oximetry, and intermittent noninvasive blood pressure (NIBP) monitoring continued. Following the administration of hydroxyethyl starch 500 ml IV and under complete aseptic precaution, lumbar epidural was performed in a flexed sitting position. Before raising a midline wheal with 1% lignocaine, the epidural space was identified using classical technique eliciting loss of resistance at L2–L3 or L3–L4 interspace. Before the insertion of epidural catheter, baseline recording of labor pain was assessed with 100 mm visual analog scale (VAS: 0–100). Following this, epidural catheter was advanced 4 cm into the epidural space. The patients then received a test dose of 3 ml of 1.5% lidocaine with 1: 200,000 epinephrine. Following the test dose, the patient was given one of the three injections through epidural catheter. After catheter placement, the patient was placed in the supine position with a left uterine displacement and 30° elevation of the head end of bed.

The parturient was randomly allocated into one of the three study groups to receive designated drugs in a total volume of 12 ml through epidural catheter. Patients in Group A (n = 30) received butorphanol 1 mg and neostigmine 7 μg/kg. Patients in Group B (n = 30) received sufentanil 10 μg and neostigmine 7 μg/kg, and patients in Group C (n = 30) received neostigmine 7 μg/kg and 0.9% normal saline.

The parameters were recorded and collected by an anesthesiologist who was blinded to the patients’ group allocation. Maternal and fetal parameters were continuously monitored throughout the labor. Maternal NIBP, heart rate (HR), and oxygen saturation (SpO₂) were continuously monitored. Fetal HR (FHR) was also continuously recorded on a cardiotocography by an obstetrician who was also blinded to the study group. Labor pain was assessed using VAS pain score and was recorded at 5, 10, 15, 20, and 30 min after the epidural injections. A VAS pain score of 30 (out of 100) or less was kept as the target. Sensory block and the motor block in the lower limb (modified Bromage scale: From 1 = complete motor blockade; 2 = almost complete motor block: patient able to move the feet only; 3 = partial motor block: patient able to move the knees; 4 = detectable weakness of hip flexion: patient able to raise the leg but is unable to keep it raised; 5 = no
detectable weakness of hip flexion: patient able to keep the leg raised for 10 s at least; 6 = no weakness at all) were recorded at 15 and 30 min after the epidural injection. The duration of analgesia was considered the time elapsed to the patient's first request for further analgesia. From that second epidural injection until delivery, the maintenance of analgesia was provided by continuous infusion with bupivacaine 0.0625% (8–10 ml/h) and rescue doses as needed.

The total duration of labor from the time of the first epidural injection until delivery, the mode of delivery (cesarean section, vaginal instrumentation, or spontaneous), and cervical dilatation at the time of second epidural injection was recorded. Maternal adverse effect and fetal side effect were also closely monitored. Sedation was graded on four-point scale: awake, drowsy, dozing (eyes shut intermittently), or asleep (but arousable on being spoken to). Maternal hypotension was defined as decrease in systolic BP (SBP) of at least 20% from the baseline and was treated by giving another 250 ml of hydroxyethyl starch IV and/or ephedrine 6 mg IV. Fetal bradycardia was defined as an FHR value between 80 and 100 bpm during 3–5 min. After delivery, neonatal Apgar score was recorded at 1 and 5 min. Number of neonates with Apgar score ≤7 at 1 and 5 min were recorded in each group. The total consumption of bupivacaine throughout the course of labor was also calculated. After delivery, overall maternal satisfaction with epidural analgesia was recorded by the patient on a four-point satisfaction scale as excellent, good, fair, or poor.

The primary outcome measure was total duration of analgesia; whereas, secondary outcomes were VAS pain score, duration of labor, total consumption of bupivacaine for maintenance of analgesia, mode of delivery, and maternal or fetal adverse effects in between the two groups.

Sample size calculation and statistical analysis
Sample size calculation was based on the previous study involving epidural neostigmine for labor analgesia. We had considered 30% increase in the duration of analgesia as clinically significant when taken from the first epidural injection till the time of the first top up till the first request for further analgesia. A priori, 28 patients were required for each group assuming an α-value of 0.05 and power of 80%. Hence, we had taken thirty patients in each group and a total of ninety patients in three groups.

Statistical analysis was done using SPSS (IBM Corp. Armonk, NY) statistical software, and the P < 0.05 was taken as statistically significant. A one-way analysis of variance (ANOVA) with post hoc Tukey’s test was used to compare the mean value among the three groups for age, height, weight, gestational age, and cervical dilatation. Repeated measure ANOVA was used to compare mean difference among the time points and also the trend among the various time points for maternal SBP, diastolic BP (DBP), maternal HR, respiratory rate, SpO₂, VAS pain score, and FHR was calculated. Post hoc Tukey test was used for inter-group comparison of hemodynamic parameters and mean VAS pain score.

RESULTS
Patients’ characteristics
The demographic characteristics in terms of age, weight and height, mean period of gestation, and cervical dilatation at the time of initiation of lumbar epidural block were comparable between the three groups and are shown in Table 1.

Maternal hemodynamic parameters
Maternal hemodynamic parameters, which included noninvasive SBP, DBP, HR rate, did not differ among groups and remained clinically stable in all the three groups until 30 min after the first epidural administration. There was a linear decrease in all the three groups with respect to SBP, DBP, and HR (P < 0.001). Respiratory rate and SpO₂ remained within normal limits in all the three groups at baseline and until 30 min of epidural administration. On inter-group comparison among the groups, the mean SBP, DBP, and HR were not found to be significant at any time point [Table 2].

Assessment of block characteristics
The level of sensory block assessed at 15 and 30 min after epidural administration were similar in different groups. No motor impairment was observed in any group at 15 and 30 min. The cervical dilatation before first and second administration was comparable in all the three groups [Table 3].

Assessment of analgesic effect
There was a linear trend decrease in the VAS pain score in all the three groups at various time points (P < 0.001, F = 606.274, df = 1, 87). Overall, Group C was significantly different as compared to Groups A and B. There was no statistically significant difference between Groups A and B (P > 0.05). At baseline and up to 5 min, no significant difference in VAS score was observed in any of the three groups; however, after 10 min and up to 30 min, there was a significant difference in Group C as compared to Groups A and B (P = 0.003, F = 6.368, df = 2, 87) [Table 4].

Moreover, significant reduction in the VAS pain score (as defined by VAS ≤30) after giving epidural analgesia was seen at 10 min in Group A and B, whereas similar reduction in VAS was seen at 20 min in Group C. On inter-group comparison among the groups, the mean VAS pain score was not found to be significant at any time point.

Duration of analgesia
The time elapsed to the patient’s first epidural top-up was considered as the duration of analgesia. The duration of analgesia was 83.67 ± 25.89 min in Group A, 111.67 ± 24.51 min in Group B, and 32.50 ± 8.88 min in Group C [Table 5]. There was a statistically significant longer effect of analgesic drug in Group B with respect to Group A and C (P < 0.001). The parturient in Group C had minimum duration of analgesia [Table 5].

Total consumption of bupivacaine
From the first epidural top-up till delivery, the maintenance of analgesia was provided by continuous infusion with
bupivacaine 0.0625% (8–10 ml/h) and rescue doses as needed. The total consumption of bupivacaine in Group A was 11.88 ± 13.67 mg, in Group B was 7.71 ± 6.90 mg and in Group C was 26.04 ± 10.36 mg [Table 6]. The consumption of bupivacaine was statistically significant in Group C as compared to Groups A and B (P < 0.001) [Table 6].

**Duration of labor and mode of delivery**
The total duration of labor and mode of delivery were comparable among the three groups. Cesarean section was done in two parturient (6.6%) in Group A, three parturient (9.9%) each in Group B and Group C respectively. Instrumental delivery was done in three parturients (9.9%) each in Group A and B and two parturient (6.6%) in Group C. Rest of the parturient in the three groups had normal spontaneous vaginal delivery [Table 7].

**Fetal adverse effects**
No harmful fetal side effects, for example, fetal bradycardia and low Apgar score were noted during labor in any of the groups. No neonate had to be admitted to the Neonatal Intensive Care Unit [Table 8].

**Fetal heart rate changes before and after epidural administration**
FHR was continuously recorded using a cardiotocography. Statistically, there was no significant difference in FHR after administration of epidural drug in the groups up to 30 min and also till delivery [Table 9].

**Maternal adverse effects**
Epidural analgesic solution did not induce particular side effects in the mother or fetus. Table 10 shows the incidence of maternal hypotension and side effects such as pruritus, nausea, vomiting among the three groups. Pruritus was managed simply by verbal reassurance in all the patients. Nausea/vomiting was managed by injection ondansetron (0.15 mg/kg) IV [Table 10].

**Maternal satisfaction**
Overall, 80% parturient in Group A and B had graded their satisfaction as excellent or good. However, the corresponding value in Group C was only 50% [Table 11].

**DISCUSSION**
The results of the present study show that epidural neostigmine 7 µg/kg combined with sufentanil 10 µg produces safe and effective analgesia in early labor in terms of duration of analgesia and maternal and fetal side effects when compared to the 7 µg/kg neostigmine combined with 1 mg butorphanol and 7 µg/kg epidural neostigmine alone. In the present study, the analgesia provided with butorphanol as an adjuvant with neostigmine has not been found to be superior to the sufentanil. The total duration of analgesia and reduction in the VAS pain scores at various time points in initial 30 min was observed to be significantly higher in the sufentanil group when compared to the butorphanol group. However, the maternal hemodynamics, duration of labor, fetal/maternal effects, incidence of instrumental deliveries/cesarean section, and maternal satisfaction remained comparable between the two groups.

Various approaches and modalities have been tried to relieve the labor pain.[13–16] However, selective analgesia or mobile epidural is extremely popular and currently the technique of choice for providing labor analgesia.[17] The use of neostigmine as an adjuvant in neuraxial anesthesia is associated with a

### Table 1: Patient characteristics

| Groups          | (n=30) | (n=30) | (n=30) | P  |
|-----------------|--------|--------|--------|----|
| Age (year)      | 23.60 ±2.93 | 22.87±2.33 | 23.47±3.04 | 0.556* |
| Weight (kg)     | 58.30 ±1.78 | 58.63±2.55 | 57.20±3.48 | 0.104* |
| Height (cm)     | 152.57±3.23 | 150.77±4.69 | 151.07±2.94 | 0.107* |
| Gestational age (weeks) | 38.43±1.45 | 37.90±0.99 | 38.30±1.21 | 0.225* |
| Cervical dilatation (cm) | 4.08±0.47 | 3.98±0.50 | 4.02±0.46 | 0.729* |

*P<0.05

### Table 2: Comparison of maternal hemodynamic parameters

| Groups | T0  | T5  | T10 | T15 | T20 | T25 | T30 | P  | P value for trend |
|--------|-----|-----|-----|-----|-----|-----|-----|----|------------------|
| SBP    |     |     |     |     |     |     |     |     | P=1.138×10^-10  |
| Group A| 130.27±5.79 | 127.00±4.89 | 124.80±5.00 | 121.47±7.28 | 118.33±7.37 | 116.83±6.91 | 116.27±6.49 | P=0.001 linear trend |
| Group B| 131.27±5.20 | 129.73±5.84 | 125.20±6.45 | 124.13±4.93 | 119.47±4.93 | 119.47±4.93 | 117.73±4.32 | F=30.152 |
| Group C| 132.13±6.91 | 126.93±5.16 | 126.60±4.96 | 125.20±4.16 | 122.53±2.73 | 119.53±2.45 | 118.80±4.12 | df=2, 87 |
| DBP    |     |     |     |     |     |     |     |     | P=1.74×10^-9   |
| Group A| 77.80±6.42 | 76.00±6.28 | 72.60±4.52 | 71.53±4.57 | 69.53±3.45 | 69.40±5.01 | 69.10±4.09 | P=0.001 linear trend |
| Group B| 78.43±2.55 | 76.00±2.41 | 73.20±1.63 | 72.47±1.46 | 71.13±1.72 | 71.00±1.80 | 70.47±2.27 | F=25.656 |
| Group C| 77.53±3.47 | 77.40±3.41 | 73.67±2.97 | 71.47±3.36 | 68.10±3.00 | 67.72±2.78 | 67.73±2.57 | df=2, 87 |
| HR     |     |     |     |     |     |     |     |     | df=1, 87 |
| Group A| 85.43±8.25 | 84.20±8.43 | 78.93±8.43 | 80.10±9.06 | 78.43±8.35 | 76.63±8.07 | 76.93±7.29 | P=0.0020 |
| Group B| 86.67±3.90 | 84.23±5.37 | 79.60±5.57 | 77.23±5.48 | 79.23±4.33 | 78.40±6.20 | 75.33±4.99 | F=6.686 |
| Group C| 87.70±2.68 | 87.30±2.83 | 84.20±4.67 | 81.83±3.05 | 80.73±2.43 | 79.20±2.68 | 76.47±5.24 | df=2, 87 |

On inter-group comparison among the groups using post hoc Tukey’s test, the mean SBP, DBP, and HR were not found to be significant at any time point. Group A=Butorphanol 1 mg and neostigmine 7 µg/kg, Group B=Sufentanil 10 µg and neostigmine 7 µg/kg, Group C=Neostigmine 7 µg/kg and 0.9% normal saline. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate.
reduction in the dose of local anesthetic during labor analgesia. Neostigmine is only recommended for epidural administration as intrathecal use significantly increases the incidence of maternal nausea and vomiting. A meta-analysis of RCTs by Cosu et al. has concluded that use of epidural neostigmine for labor analgesia is associated with a decrease in the risk of pruritus with no increase in the incidence of hypotension, dizziness, or sedation and no effect on the incidence of abnormal FHR patterns or Apgar scores.[11]

However, it has been observed that epidural neostigmine alone, even at a dose of 750 μg (i.e., 8–9 μg/kg), does not provide satisfactory pain relief in the first stage of labor. This can be attributed to various reasons. First, as a consequence of the hydrophilic nature of the compound, the dose reaching the spinal cord should be at least 100 μg to provide some analgesia in volunteers. Furthermore, in humans, painful labor does not seem to activate spinal cholinergic pathways. Second, neostigmine has been reported to be more effective to relieve pain of somatic origin than of visceral origin, and the first stage of labor mostly implies visceral pain. Due to the aforementioned reasons, an adjuvant is desirable for satisfactory and prolonged pain relief in the first stage of labor. An opioid-adjuvant which is very commonly studied with epidural neostigmine for providing labor analgesia is sufentanil. The dose combination of epidural neostigmine with sufentanil which has been found to be effective for labor analgesia is 7 μg/kg and 10 mg, respectively. Hence, a similar dose combination has been used in the present study.

In the present study in the epidural neostigmine with sufentanil group, the analgesia obtained was the best, i.e., the VAS pain score <30 was achieved within 10 min in 63.3% of parturient and within 15 min in 83.3% parturient, the average duration of analgesia being 111.67 ± 24.51 min without motor block or any other side effect in mother and fetus. These results are consistent with the results by Roelants et al.[16] Roelants and Lavand’homme in 2004 concluded that selective labor analgesia occurred within 10 min in 72% parturient and within 15 min in 85% parturient with an average duration of 119 min using a combination of epidural sufentanil 10 μg with neostigmine 500 μg. In this study the epidural combination with neostigmine 250 μg was found to be ineffective; whereas, 750 μg did not produce higher effect than 500 μg.

Similarly, butorphanol has also been found to be a safe drug in adjuvant. Butorphanol in the dose of 1 or 2 mg has been found to be a safe and effective adjuvant in combination with bupivacaine for labor analgesia.[12] Abboud et al. was concluded that adding small doses of butorphanol (1 mg) to epidural lidocaine during labor is effective and safe.[13] However, Hunt et al. studied the dose response of butorphanol in combination with 0.25% bupivacaine for labor analgesia and concluded that the optimal dose of butorphanol was 2 mg as it provided significantly better analgesia and earlier time to onset of analgesia than when no butorphanol was added.[17] Butorphanol has been comparatively under-studied for labor analgesia, and it has never been studied in combination with epidural neostigmine for labor analgesia.

In the present study, we have used 1 mg butorphanol as an adjuvant in combination with 7 μg/kg neostigmine and this combination has not been found to be superior to the sufentanil. The duration of analgesia and reduction in pain in

| Table 3: Assessment of block characteristics resulting from single epidural injection |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Sensory level at 15 min (mode [range])          | Group A         | Group B         | Group C         |
| T10 (T9-11)                                    | T9 (T8-11)      | T11 (T10-12)    |
| Sensory level at 30 min (mode [range])         | T9 (T9-11)      | T10 (T8-11)     | T11 (T10-12)    |
| Motor block at 15 min (modified Bromage scale) | 6               | 6               | 6               |
| Motor block at 30 min (modified Bromage scale) | 6               | 6               | 6               |
| Cervical dilation before first administration of epidural (cm)* | 4.08±0.47 | 3.98±0.50 | 4.02±0.46 |
| Cervical dilation before second administration of epidural (cm) | 5.45±0.59 | 5.47±0.73 | 5.01±0.71 |

P>0.05 by one-way ANOVA for cervical dilation before first and second administration. Group A=Butorphanol 1 mg and neostigmine 7 μg/kg, Group B=Sufentanil 10 μg and neostigmine 7 μg/kg, Group C=Neostigmine 7 μg/kg and 0.9% normal saline. *P>0.05 (not significant) between groups. ANOVA=Analysis of variance

| Table 4: Evolution of pain scores at various time intervals after epidural administration in different groups of parturient |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Groups                                         | T0              | T5              | T10             | T15             | T20             | T25             | T30             | P              | P value for trend |
| Group A                                        | 90.67±12.29     | 53.00±24.79     | 28.33±18.39     | 20.00±19.29     | 17.00±15.34     | 17.00±16.33     | 19.33±16.38     | P=0.003        | P=0.001 linear trend |
| Group B                                        | 93.00±11.49     | 56.00±32.22     | 27.33±23.18     | 19.67±19.38     | 17.67±14.06     | 17.33±14.60     | 16.50±13.76     | F=6.368        | F=606.27 linear trend |
| Group C                                        | 93.00±9.15      | 57.67±27.50     | 46.67±30.77     | 37.33±24.76     | 28.67±22.55     | 28.67±19.95     | 30.67±21.48     | df=2, 87       | df=1, 87 linear trend |

On inter-group comparison among, the groups using post hoc Tukey’s test, the mean VAS pain score was not found to be significant at any time point. Group A=Butorphanol 1 mg and neostigmine 7 μg/kg, Group B=Sufentanil 10 μg and neostigmine 7 μg/kg, Group C=Neostigmine 7 μg/kg and 0.9% normal saline, T0=Baseline, T5; T10; T15; T20; T25; T30 after 5, 10, 15, 20, 25, and 30 min after the first epidural drug administration, respectively. VAS=Visual analog scale
at various time points in the initial 30 min were observed to be significantly higher in the sufentanil group when compared to the butorphanol group. However, the reduction in the VAS pain scores, maternal hemodynamics, duration of labor, fetal/maternal effects, incidence of instrumental deliveries/caesarean section and maternal satisfaction remained comparable between the two groups.

In the present study, only one patient (3.3%) in the sufentanil group had pruritus. Similar to our result, in a study by Roelants and Lavand’homme, no case of pruritus was reported in the groups in which a combination of neostigmine (250–750 µg) and sufentanil (10 µg/kg) was administered,[9] whereas, a high incidence, i.e., 20% was reported in the laboring patients in whom only neuraxial sufentanil was used and that too in a high dose, i.e., 20 µg/kg.

The duration of labor remained comparable in between the three groups, and the incidence of instrumental delivery and caesarean section was reported to be 6%–9% for each in all the three groups. On the contrary, Roelants and Lavand’homme, reported 0% incidence of instrumental delivery and cesarean section with combination of sufentanil 10 µg and neostigmine 250/500 µg and only 4% incidence with a combination of sufentanil 10 µg and neostigmine 750 µg.[9] However, in the same study, the incidence of instrumental delivery was as high as 12% with sufentanil (10 µg) and 8% with sufentanil (20 µg) alone.

None of the parturients developed hypotension or respiratory depression in any group. Sedation has been reported equally with all the three drugs used in the study, i.e., 3.3% or one patient in each group. On the contrary, the incidence of sedation reported by Pokharel et al.[14] was 5% in patients in whom epidural butorphanol was given along with bupivacaine for postoperative pain relief after cesarean delivery. However, Shrestha et al.[19] did not report any adverse maternal outcome in parturients who received 2 mg butorphanol along with 10 ml of 0.1% bupivacaine for analgesia during labor.

FHR was continuously recorded using cardiotocography. Statistically, there was no significant difference in FHR after administration of epidural drug in any of the groups in the initial 30 min and also till the delivery. No harmful fetal side effects, for example, fetal bradycardia and low Apgar score

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**Table 5: Duration of analgesia**

| Groups          | Group A (n=30) | Group B (n=30) | Group C (n=30) | P  |
|-----------------|----------------|----------------|----------------|----|
| Mean±SD (min)   | 83.67±25.89    | 111.67±24.51   | 32.50±8.88     | <0.001 |
| Range           | 20-125         | 60-160         | 15-45          |    |

**Table 6: Duration of labor and mode of delivery**

| Groups          | Group A (n=30) | Group B (n=30) | Group C (n=30) | P  |
|-----------------|----------------|----------------|----------------|----|
| Duration of labor, mean±SD (h) | 5.22±3.36 | 5.10±1.36 | 5.14±1.68 |
| Mode of delivery (%) | Instrumental: 3 (9.9) | 3 (9.9) | 2 (6.6) |
| Cesarean section | 2 (6.6) | 3 (9.9) | 3 (9.9) |
| Spontaneous     | 28 (83.3) | 30 (82.6) | 25 (83.3) |

**Table 7: Fetal adverse effects**

| Adverse effects       | Group A (n=30) | Group B (n=30) | Group C (n=30) |
|-----------------------|----------------|----------------|----------------|
| Fetal bradycardia     | 0              | 0              | 0              |
| Apgar score ≤7 (min)  |                |                |                |
| At 1                  | 0              | 0              | 0              |
| At 5                  | 0              | 0              | 0              |
| ICU admission         | 0              | 0              | 0              |

Values are number of patients as percentage in parentheses. Group A=Butorphanol 1 mg and neostigmine 7 µg/kg, Group B=Sufentanil 10 µg and neostigmine 7 µg/kg, Group C=Neostigmine 7 µg/kg. ICU=Intensive Care Unit

**Table 8: Maternal adverse effects**

| Adverse effects | Group A (n=30) | Group B (n=30) | Group C (n=30) |
|-----------------|----------------|----------------|----------------|
| Hypotension     | 0              | 0              | 0              |
| Pruritus (%)    | 0              | 1 (3.3)        | 0              |
| Nausea/vomiting (%) | 1 (3.3) | 0              | 2 (6.6) |
| Respiratory depression | 0            | 0              | 0              |
| Sedation (%)    | 1 (3.3)        | 1 (3.3)        | 1 (3.3)        |

Values are number of patients as percentage in parentheses. Group A=Butorphanol 1 mg and neostigmine 7 µg/kg, Group B=Sufentanil 10 µg and neostigmine 7 µg/kg, Group C=Neostigmine 7 µg/kg and 0.9% normal saline, T0=Baseline, T5, T10, T15, T20, T25, T30 after 5, 10, 15, 20, 25 and 30 minutes after 1st epidural drug administration respectively

**Table 9: Fetal heart rate changes before and after epidural administration**

| Groups          | Time interval (min) | P      |
|-----------------|---------------------|--------|
|                 | T0                  | T5     | T10    | T15    | T20    | T25    | T30    |        |
| Group A         | 139.10±5.57         | 139.72±5.95 | 139.20±5.71 | 138.07±4.98 | 138.73±4.38 | 140.27±4.93 | 139.37±4.86 | 0.05    |
| Group B         | 146.73±7.25         | 143.03±6.40 | 142.83±5.22 | 141.83±4.79 | 142.33±3.87 | 140.90±4.25 | 141.57±3.87 | 16.123  |
| Group C         | 139.10±4.01         | 139.67±4.15 | 139.63±4.64 | 139.47±4.79 | 141.47±4.66 | 141.33±3.84 | 141.20±4.72 | 2.87    |

Data are expressed as mean±SD. Group A=Butorphanol 1 mg and neostigmine 7 µg/kg, Group B=Sufentanil 10 µg and neostigmine 7 µg/kg, Group C=Neostigmine 7 µg/kg and 0.9% normal saline, T0=Baseline, T5, T10, T15, T20, T25, T30 after 5, 10, 15, 20, 25 and 30 minutes after 1st epidural drug administration respectively.
Table 10: Maternal adverse effects

| Adverse effects          | Group A (n=30) | Group B (n=30) | Group C (n=30) |
|--------------------------|----------------|----------------|----------------|
| Hypotension              | 0              | 0              | 0              |
| Pruritus                 | 0              | 1 (3.3%)       | 0              |
| Nausea/vomiting          | 1 (3.3%)       | 2 (6.6%)       | 0              |
| Respiratory depression   | 0              | 0              | 0              |
| Sedation                 | 1 (3.3%)       | 1 (3.3%)       | 1 (3.3%)       |

Values are number of patients as percentage in parentheses. Group A=Butorphanol 1 mg and neostigmine 7 µg.kg⁻¹, Group B=Sufentanil 10 µg and neostigmine 7 µg.kg⁻¹, Group C=Neostigmine 7 µg.kg⁻¹.

Table 11: Maternal satisfaction

| Maternal satisfaction | Group A (n=30) | Group B (n=30) | Group C (n=30) |
|-----------------------|----------------|----------------|----------------|
| Excellent             | 15 (50%)       | 17 (56.6%)     | 6 (20%)        |
| Good                  | 9 (30%)        | 7 (23.3%)      | 9 (30%)        |
| Fair                  | 5 (16.6%)      | 4 (13.3%)      | 8 (26.6%)      |
| Poor                  | 1 (3.3%)       | 2 (6.6%)       | 7 (23.3%)      |

Values are number of patients as percentage in parentheses. Group A=Butorphanol 1 mg and neostigmine 7 µg.kg⁻¹, Group B=Sufentanil 10 µg and neostigmine 7 µg.kg⁻¹, Group C=Neostigmine 7 µg.kg⁻¹.

were noted during labor in any of the three groups. No neonate had to be admitted to the Neonatal Intensive Care Unit.

CONCLUSION

Epidural combination of sufentanil (10 µg) with neostigmine (7 µg.kg⁻¹) provided better analgesia in terms of longer duration of analgesia and significant reduction in the VAS pain scores at various time points in the first 30 min of the administration of the epidural drugs when compared to the epidural combination of butorphanol (1 mg) with neostigmine 7 µg.kg⁻¹. However, both combinations using sufentanil and butorphanol as adjuvants with epidural neostigmine provided early onset and longer duration of analgesia when compared to the epidural neostigmine alone. In addition, both the adjuvants (sufentanil 10 µg or butorphanol 1 mg) with epidural neostigmine did not produce any significant impact on the total duration of labor or the mode of delivery. None of the epidural analgesic solutions induced any maternal or fetal side effects.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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