A Comparative Study of Two Different Doses of Fentanyl Added to Bupivacaine for Intermittent Epidural Labor Analgesia: A Prospective Randomized Double Blind Study

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Abstract

Background: Intermittent technique of labor epidural analgesia has been showing promising results over other techniques. This study was to assess and compare efficacy of two different doses of fentanyl mixed with low doses of bupivacaine in intermittent labor epidural analgesia.

Methods: 90 ASA grade I-II parturients in active labor with a cervical dilatation of 3 to 5 cm were randomly allocated to three different groups-

- **Group A**: 10ml Bupivacaine 0.125% + fentanyl 10µg (1µg/ml).
- **Group B**: 10ml Bupivacaine 0.125% + fentanyl 20µg (2µg/ml).
- **Group C**: 10ml Bupivacaine 0.125% (The control group).

All patients were preloaded with 10-15ml/kg Lactated Ringer’s solution. Labor analgesia was maintained by intermittent boluses of the drug combination.

Results: The mean time of onset of analgesia was significantly lower (P<0.05) and the duration of analgesia was significantly higher (p<0.01) in Group B when compared with Group A and group C (p<0.001). The patients satisfaction was considerably better observed in Group B (p<0.01). However in both group’s progression of labor was found to be slightly prolonged than group C. The level of sensory and the motor block was comparable in both the groups was at T8-T10 level and it was comparable and level of motor blockade (bromage score=0, 1) in each group was also not significant (p>0.05).

Conclusion: Addition of fentanyl (2µg/ml) to bupivacaine 0.125% decreases the time of onset of analgesia and increases the duration of analgesia and level of maternal satisfaction during labor as compared to fentanyl (1µg).

Keywords: Labor analgesia; Fentanyl; Intermittent epidural technique

Introduction

The joy of child birth is always accompanied with a fear of pain. A negative birth experience is associated with subsequent infertility, and women’s experiences should therefore be considered seriously in the provision of maternity care [1]. Concept of walking epidural during labor is worthwhile as confining a parturient to bed may lead to painful and prolonged labor with higher incidences of abnormal presentations and foetal distress [1,2]. Now a days its considered to be gold standard for labor pains. Epidural analgesia has been used extensively in developed countries and now getting popular in developing countries like India etc. with some modification in traditional epidural technique.

Over the past ten years there have been remarkable changes in the field of obstetric anaesthesia. Anaesthesiologists have improved upon their techniques to alleviate pain during labor while at the same time increasing the safety for both mother and the baby. Newer techniques such as combined spinal-epidural, continuous epidural infusions, walking epidurals and patient controlled epidural analgesia (PCEA) are now available.

On the contrary continuous infusion epidural analgesia (CIEA) has been associated with significant motor blockade [3]. However newer modalities like CSE, PCEA are more expensive, technically more difficult and associated with an increased incidence of side effects like nausea, vomiting, pruritus along with use of opioids [4]. Although rarely with meningitis also been reported [5].

The greatest advantage of implementing intermittent lumbar epidural for labor analgesia is the lack of need of volume elastomeric epidural infusion pump; making its worth role in conducting deliveries in emergency settings, primary, secondary and tertiary health centres of developing countries (india etc.) where these facilities are not easily available but do have the human resources to provide the intermittent top-ups.

Our study was designed to evolve a appropriate dose combination of bupivacaine and fentanyl in extradural labor analgesia using

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intermittent boluses technique and to evaluate the maternal and neonatal outcomes with its effect on progress of labor.

**Patient and Methods**

**Ethical consideration**

After obtaining approval from the institutional ethics committee, the present study was conducted after taking informed written consent from all the parturients.

90 patients were randomly assigned to one of the two intervention groups A, B and C:-

(GROUP A; n=30) : 10 ml of 0.125% Bupivacaine and 1µg/ml fentanyl as a first bolus followed by intermittent top ups of 0.0625% bupivacaine 10ml + fentanyl 1µg/ml at VAS≥3.

(GROUP B; n=30) : 10 ml of 0.125% Bupivacaine and 2µg/ml fentanyl as a first bolus followed by intermittent top ups of 0.0625% bupivacaine 10ml + fentanyl 2µg/ml at VAS≥3.

(GROUP C; n=30): 10 ml of 0.125% Bupivacaine as a first bolus followed by intermittent top ups of 0.0625% bupivacaine 10ml at VAS≥3.

Patients were explained regarding the possible risks and complications. Women were placed in left lateral position when cervix was 3-5cm dilated and with strict aseptic precautions, mid lumbar epidural space L3-L4/L4-L5 was identified by using a loss of resistance technique with a 16-18G tuohy needle and a epidural catheter (B. Braun, perifix 16G or 18G catheter, Melsunghen) was sited 4-5cm in the space. Epidural test dose was avoided from the study.

**Study Type-** Cross sectional hospital based study.

**Study Duration-** 10th August 2009 to 10th December 2009.

**Study Subjects-** 90 patients admitted in the obstetric labor room were selected for the study.

**Sampling Technique-** Time Based Simple Random Sampling. Subject and other study personnel were blinded as to group assignment.

**Selection of Sample-** During the study duration, out of 200 cases 90 patients were selected for the study by using simple random sampling.

- **Inclusion criteria-** Full term (37-42 wks) parturient of ASA class I and II having fixed cephalic presentation and cervical dilatation of 3 to 5 cm in spontaneous labor were enrolled for the study.
- **Exclusion criteria-** Parturient with PIH, preterm labor, breech presentation, h/o previous cesarean delivery, bad obstetric history, bleeding dyscrasia, spinal deformities, patient on anticoagulants, hypotensive patient, morbid obese and elderly patient>35 years and patient having cervical dilatation>5cm before epidural catheter insertion, patient having allergy to local anesthetics and opioid, and refusal on consent agreement were excluded from this study.

**Data collection**

For the collection of sample all the variables were assessed and a pretested semi structured Performa was used containing information regarding sociodemographic details of patient variables.

- **Preoperative data collection-** A complete pre-anaesthetic evaluation was carried out, maternal baseline pulse rate, blood pressure, respiratory rate and SpO2, and foetal heart rate were recorded.
- **Drug preparation and top-up administration-** Drug solution containing analgesic was prepared by OT assistant or junior resident. The top-up administration on request of analgesia by the parturient by recording VAS was given by the resident (junior/ senior) on duty. These were completely blinded from the study.

**Data processing and analysis**

After collection, data's were put in excel sheet and SPSS 17th version and analyzed with the intention to treat.

**Statistical analysis used**

The statistical significance for categorical variables was determined by Chi-square analysis. Fisher exact t-test was used in case one or more expected cell count was less than 5. For continuous variables two sample t-test was applied. Differences among the group means were compared using analysis of variance. Results were expressed as Mean ± SD (standard deviation). A P value <0.05 was considered statistically significant.

Taking sample size of 30 in each group with a =0.05, the power of study is approximately 80%.

In group A (n=30), first dose of 10ml containing 0.125% bupivacaine mixed with 1mcg/ml fentanyl (0.0001%) was administered via the catheter into the epidural space. In group B (n=30) first dose containing similar concentration of bupivacaine along with 2mcg/ml fentanyl (0.0002%) was given. Top up doses (10ml containing 0.0625% bupivacaine with similar concentration of fentanyl respective to each group) are given when patient VAS≥3. After each drug administration patient vitals (pulse, B.P ., RR, SPO2), maximum sensory/motor blockade level achieved and foetal heart rate were monitored at 5, 10, 15, 30, 45, 60, 90, 120, 150, 180 min interval or till delivery. Following every top up dose, patients were monitored carefully for 10min to detect any weakness or inadequacy of analgesia.

Motor blockade was assessed by Modified Bromage score [6] (0=no impairment; 1=unable to raise extended leg but able to move knees and foot; 2=unable to raise extended leg as well as flex knees, but able to move foot; 3=not able to flex ankle, feet or knees) was determined every 60 min during first stage of labor. Maximum level of sensory blockade achieved assessed by pin-prick method.

**Observed parameters were**

- Onset of analgesia, duration of analgesia and time to first top up requirement was assessed by VAS for pain at every 10min, no of top ups required, duration of first and second stage of labor, mode of delivery, APGAR score at 1 and 5 min.
- On the day after delivery, maternal satisfaction level assessed by parturient acceptance regarding quality of analgesia throughout labor was assessed by following scoring system: 0-failure, 1-incomplete, 2-good, 3-excellent, NPE (not possible to evaluate) due to delivery by cesarean section [6,7]. All the obstetricians, attending the parturient were asked regarding maintenance of maternal expulsive power during second stage of labor.

**Results**

Onset and duration of analgesia when compared to the intervention groups A and B was found to be statistically significant (P value<0.0001). Twenty parturients in group B had profound analgesia with in 10 min, in group A, it took around 15-20 min to achieve maximum analgesia...
while in group C, maximum analgesia seen after 20-30 min (Table 4). VAS (visual analogue score) and VPS (verbal pain score) showed a faster onset of complete analgesia in group B. Duration of analgesia of first bolus dose (time interval in between bolus dose to first maternal analgesia request) was higher with group B (i.e.120±20.26 min as compare to 100±10.04 min of group A, 75±12.24 min of group C) (Table 3).

Duration and progression of labor (first and second stage) from insertion of epidural (i.e. Study time) was found to be slightly prolonged by approximately less than 15 min in group B as compared with group A and C that was statistically non significant(P value >0.05). There was no difference in degree of sensory blockade as assessed by pin prick method or ice cube method, maximum at T6 level in around 60% parturients and motor blockade by modified bromage score (scored=0) in among 93.34% in group A and 90% parturients of group C that means they were able to walk up to a certain distance and were able to void by themselves. Only two parturients in group A and three parturient in group B had a score=1 as compared to eight (26.67%) parturients of the control group that was statistically significant (P value=0.024) (Table 4). APGAR scores at 1 and 5 min were found to be comparable and statistically non significant in both intervention groups (P value=0.99) (Table 4). Top up requirements because of shorter duration of action, was quite higher in control group C than intervention group A and B in the order of C>A>B. (P value=0.001) (Table 3).

The total dose of bupivacaine and fentanyl used in our study was 67.42±20.25 mg bupivacaine and 74.34±30.34mcg fentanyl in group A and 53.20±18.15 mg bupivacaine and 65.12±25.65 mcg fentanyl in group B and 76.24±12.34mg bupivacaine in the control group C which was statistically significant (P value<0.05) (Table 3).

There was one accidental dural puncture in group B and the patient was excluded from the study.

Mode of delivery spontaneous i.e. normal vaginal (N.V.D.) in both of the intervention groups, only one patient in group A (3.33%), two in group B (6.66%) and four parturient in group C (13.34%) were converted to caesarean section because of the prolongation of the labor i.e. statistically non- significant (P value=0.337).

Maternal nausea and vomiting were reported in two cases (6.66%) in group B and in one parturient (3.33%) in group A as compared to nil among control group C (Table 4). Incidence of urinary retention (13.34%) and hypotension (6.66%) were quite higher in control group than any intervention group. Foetal distress was reported in one foetus in group A and C (3.33%), two in group B (6.66%). Maternal satisfaction level was significantly higher (90%) in group B, twenty parturient reported excellent analgesia, while seven explained good score; when compared to 60% satisfaction level in group A and just 40% in the control group (P value<0.0001) (Table 4).

Discussion

In this prospective randomized double blind study between two different doses of fentanyl for labor analgesia, doses chosen were based on a pilot study assessing clinical impression of efficacy, motor blockade, and duration of action. We decreased the volume and concentration of drug injected epidurally, keeping in view the difference in

| Parameters studied | Control Group | Intervention Groups | Test applied (Chi-squire analysis) |
|-------------------|--------------|---------------------|----------------------------------|
| ONSET OF ACTION: | GROUP C | GROUP A (B+F10) | GROUP B (B+F20) | X² value | p value |
| 0-10min           | (1.33%)     | 2(6.60%)            | 18(60%)                         | 51.01 | <0.0001 |
| 15-30min          | 26(86.67%)  | 9(30%)              | 17(56.66%)                      |        |        |
| HIGHEST SENSORY  | 2            | 3(10%)              | 18(60%)                         | 0.89  | 0.235   |
| BLOCKADE          |             | 16(53.34%)          | 19(63.33%)                      |        |        |
| T6, T8, T10       |             | 11(36.66%)          | 19(63.33%)                      |        |        |
| MAX. MOTOR BLOCKADE| 22(73.33%) | 29(96.66%)          | 27(90%)                         | 7.5   | 0.0235  |
| Mod. bromage Score| 08(26.66%) | 01(3.33%)           | 03(10%)                         |        |        |
| Score-1           |             | 01(3.33%)           | 03(10%)                         |        |        |
| MODE OF DELIVERY- | 26(86.67%)  | 29(96.66%)          | 28(93.33%)                      | 2.17  | 0.337   |
| N.V.D.            | 04(13.34%)  | 01(3.33%)           | 01(3.33%)                       |        |        |
| L.S.C.S.          |             | 02(6.60%)           | 01(3.33%)                       |        |        |
| APGAR SCORE at    | 27(90%)     | 28(93.33%)          | 28(93.33%)                      | 0.00  | 0.99    |
| 5min=+5           | 28(93.33%)  | 29(96.66%)          | 29(96.66%)                      |        |        |
| at 5min=+7        | 28(93.33%)  | 28(93.33%)          | 28(93.33%)                      |        |        |
| SIDE EFFECTS-     | - 00        | 1(3.33%)            | 2(6.60%)                        | 5.19  | 0.07    |
| (Maternal):       | - 02        | -0                  | -0                              |        |        |
| Nausea/Vomiting   | - 04        | -0                  | -0                              |        |        |
| Hypotension       |             |                    |                                 |        |        |
| Urinary retention |             |                    |                                 |        |        |
| (Foetal):         | 00           | 1(3.33%)            | 2(6.60%)                        | 2.07  | 0.355   |
| distress/bradycardia|           |                    |                                 |        |        |
| MATER. SATISFACTION LEVEL- | 12(40%) | 18(60%)            | 27(90%)                         | 33.07 | 0.0006  |
| OVERALL            | 03(10%)     | 01(3.33%)           | 02(6.60%)                       |        |        |
| FAILURE            | 03(9.99%)   | 02(6.60%)           | 01(3.33%)                       |        |        |
| INCOMPLETE         | 12(40%)     | 09(30%)             | 01(3.33%)                       |        |        |
| GOOD               | 10(30%)     | 12(40%)             | 07(23.33%)                      |        |        |
| EXCELLENT          | 02(6.60%)   | 06(20%)             | 20(66.66%)                      |        |        |

Table 1:
in demographic data (age, height) in the Indian population as compared to the western parturient (Table 1) [7-9]. Our aim was to minimising the concentration of local anaesthetic along with appropriate dose of opioid, so as to provide maximal labor analgesia along with active maternal participation during labor without affecting foetal well being.

The test dose was avoided in this study because in a laboring patient, maternal heart rate variability from the pain of uterine contractions may confuse interpretation of the heart rate response, and intravenous epinephrine may have deleterious effects on uterine blood flow [10,11].

The time interval from initial bolus dose to maternal analgesia request in our study was significantly increased in group B. The longer latency to demand for analgesia in parturient of group B could be attributed to comparatively higher concentration of opioid (fentanyl) used with diluted low concentration of local anaesthetic (bupivacaine) since an increase in doses of opioid and local anaesthetic is directly proportional to the quality and duration of satisfactory analgesia and anaesthesia but inversely to the time of onset of block [7].

The VAS and VPS at 10 min were lower in group B indicating early onset of analgesia. There was no difference in degree of motor blockade in both intervention groups.

In our study 93.33% parturient in group A and 90% in group B were mobile during for 25-50% of study time. Ambulation was achieved in 70% of fentanyl epidural group and 68% bupivacaine, epinephrine, fentanyl (BEF) group by Breen et al. [8]. The incidence of sparing of motor blockade in both intervention groups in the present study is likely explained by the use of a lower concentration bupivacaine solution. Because motor blockade is considered undesirable during labor analgesia, the potential local anaesthetic (bupivacaine) sparing effect of an intermittent bolus technique may be more clinically relevant rather than with other continuous epidural techniques like CIEA, PCEA and CSEA [3].

Several mechanisms have been proposed to explain the advantages of bolus compared with continuous infusion of epidural solutions. When injected as a bolus through a multiorifice epidural catheter, the solution exits the distal end of the epidural catheter through all the orifices [12]. In contrast, when a continuous infusion of the same volume is injected through the catheter, it primarily exits through the proximal orifice. Another possible explanation of reduced bupivacaine consumption with bolus technique may be the distribution of solutions in epidural space is non-uniform but it spreads uniformly when delivered in large volumes with high injectable pressure [13].

Our most significant findings were the reduction in number of boluses and overall reduction in local anaesthetic use in the group B (2µg/ml fentanyl) [14-16], Local anaesthetic sparing by a magnitude of 15–20% is also characteristic of patient controlled epidural analgesia (PCEA) [17] whereby patients self administer local anaesthetic according to their level of pain. However, a potential criticism of the PCEA system is that patients will only demand a bolus when developing pain as the sensory block regresses. This is compounded by the lag time between administration and action of epidural drugs. In contrast, regular intermittent bolus administration endeavours to prevent pain by injecting local anaesthetic at time intervals chosen so that the majority of patients remain pain free [17-19].

In addition to bupivacaine, we found a dose sparing effect of fentanyl [3,14,15,20,21]. Systemic absorption of epidural fentanyl may result in foetal depression [22,23]. In group B there were two reported cases of foetal bradycardia seen as compare to group A in which only one case was seen. Incidence maternal side effects like urinary retention and hypotension were quite higher in control group than any intervention group that possibly justified with the higher consumption of local anaesthetic (bupivacaine). Maternal anaesthesia satisfaction was higher (90% reported good/excellent) in group B (with fentanyl 2mcg/ml group) than in group A (fentanyl 1mcg/ml) showing 60% satisfied higher (90% reported good/excellent) in group B (with fentanyl 2mcg/ml group) showing 60% satisfied.

In summary, we found that epidural fentanyl 2µg/ml is better

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### Table 2: Comparison of Anthropometric Variables and Age of Parturient between Three Groups.

| Variables | Control Group | Intervention Groups | Test applied |
|-----------|---------------|---------------------|--------------|
| Group C   | Group A (B+F10) | Group B (B+F20) | Group C | ANOVA |
| Age (years) | 30 | 22.4 | 1.86 | 23 | 2.24 | 22 | 1.80 | F=1.94 | p=0.148 |
| Height (cm) | 30 | 154.64 | 3.24 | 156.28 | 4.22 | 155.20 | 3.84 | F=1.45 | p=0.24 |
| Weight (kg) | 30 | 54.42 | 5.20 | 56.80 | 6.40 | 55.88 | 5.90 | F=1.261 | p=0.289 |

### Table 3: Comparison of Obstetric Variables of Mothers between Three Groups.

| Variables | Control Group | Intervention Groups | Test applied |
|-----------|---------------|---------------------|--------------|
| Group C   | Group A (B+F10) | Group B (B+F20) | T-test |
| Gravida | 30 | 1.44 | 0.80 | 1.40 | 0.90 | 1.48 | 0.60 | F=0.08 | p=0.924 |
| Cervical dilatation (cm) | 30 | 3.60 | 0.90 | 3.34 | 0.87 | 3.80 | 0.94 | F=1.95 | p=0.148 |
| Baby Wt (kg) | 30 | 2.50 | 0.24 | 2.50 | 0.24 | 2.60 | 0.23 | F=1.785 | p=0.174 |

### Table 4: Comparison of Obstetric Variables of Mothers between Three Groups.

| Parameters | Control Group | Intervention Groups | Test applied |
|-----------|---------------|---------------------|--------------|
| Parameters studied | Control Group | Intervention Groups | Test applied |
| Study duration of labour (hrs.) | Group C | Group A | Group B | ANOVA |
| 1st stage | 2.76±0.34 | 2.80±0.35 | 2.87±0.36 | f=0.174 | p=0.977 |
| 2nd stage | 1.26±0.26 | 1.24±0.24 | 1.32±0.32 | f=0.001 | p=0.991 |
| Total dose Bupivacaine (mg) | 76.24±12.34 | 67.42±20.25 | 53.20±18.15 | f=13.639 | p=0.001 |
| Total dose Fentanyl (mcg) | N/A | 74.34±30.34 | 65.12±25.65 | T=2.59 | p=0.03 |
| No. of top-ups | 3.12±1.23 | 2.48±1.29 | 1.82±1.35 | f=7.606 | p=0.001 |
| Duration of Action (1st top up requirement) | 75±12.24 min | 100±10.04 min | 120±20.26 min | f=69.20 | p=0.001 |

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than 1µg/ml when combined with bupivacaine in intermittent bolus technique, as it leads to faster onset, longer duration of analgesia, higher maternal satisfaction, lesser drug requirement of local anaesthetic with comparable side effect profile.

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