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Original Research Article

Comparison between Intermittent Epidural Boluses of Levobupivacaine with Fentanyl and Ropivacaine with Fentanyl for Combined Spinal Epidural Technique in Labour Analgesia: A Double- Blinded Prospective Study

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Conflict of interest: Nil

Abstract

Background: Combined spinal epidural (CSE) analgesia is an established technique for labour analgesia. It offers "effective, rapid-onset analgesia with minimal risk of toxicity or motor block". Levobupivacaine & Ropivacaine are less cardiotoxic, long acting amide LAs.

Aims and Objective is to compare 0.125% Levobupivacaine and 0.2% Ropivacaine with fentanyl as epidural drugs for labour analgesia using CSE technique regarding time for onset & duration of analgesia of the first epidural bolus dose and to compare quality of labour analgesia, and assess the maternal and foetal outcome, incidence of instrumental delivery, study of motor blockade, haemodynamic changes, maternal satisfaction.

Methods: Following approval from Institutional Ethical committee, 50 ASA PS II pregnant women requesting for labour analgesia, satisfying the inclusion criteria were randomly divided equally into groups L & R. CSE performed, 0.5ml hyperbaric bupivacaine 0.5% with fentanyl 25mcg administered intrathecally. Intermittent boluses 10 ml of study drugs given through epidural catheter as demand dose.

Result: The mean onset of analgesia with Group R= 16.280$\pm$ 1.59 min and with Group L = 21.480$\pm$1.32 min (p=0.000). Total duration of analgesia in Group R= 72.08 $\pm$1.97 min, whereas Group L= 82.160 $\pm$2.07 min (p=0.000). There was no difference between the groups for maternal demographic traits, mode of delivery, maternal and fetal outcome and maternal satisfaction. Both 0.125% Levobupivacaine and 0.2% Ropivacaine produces excellent quality of analgesia.

Conclusion: Ropivacaine produces an early onset of analgesia than Levobupivacaine but Levobupivacaine had significant prolonged analgesia compared to Ropivacaine. Both drugs were found to be safe for labour analgesia. Maternal satisfaction and foetal outcome were similar with both the drugs.

Keywords: Combined Spinal Epidural, Labour Analgesia, Levobupivacaine, Ropivacaine

Background

Labour is one of the most painful experiences women undergo in their lifetime. Implementing effective and safe analgesia during labour is challenging.

Of all the possible methods of pain relief, neuraxial labour analgesia is most commonly used method. It is most reliable and effective method of reducing pain during labour [1]. Combined spinal epidural (CSE) technique gained popularity because of fast onset of analgesia provided by intrathecal opioids with a small dose of Local Anaesthetics (LA). The duration of analgesia can be prolonged through the use of epidural catheter [2].

For epidural, most commonly used drugs for labour analgesia are Bupivacaine, Levobupivacaine or Ropivacaine. Levobupivacaine and Ropivacaine were recently introduced drugs into the obstetric analgesia practice. Levobupivacaine is preferred over the Bupivacaine because of its reduced cardiotoxicity as well as decreased intensity of motor blockade.

After seeing in Literature, there are very few studies which have compared Levobupivacaine and Ropivacaine for Labour analgesia. Hence a study was required to compare these two drugs as epidural boluses in CSE technique in Indian population.

0.125% Levobupivacaine and 0.2% Ropivacaine are equipotent doses. Fentanyl is required to be used to look after the visceral pain and to reduce the dose of LA used in epidural analgesia. Intermittent epidural bolus has advantage of better spread of the LA in the epidural space with better analgesia. Hence the present study was undertaken to compare intermittent bolus of 0.125% Levobupivacaine and 0.2% Ropivacaine with fentanyl as epidural drugs for labour analgesia using CSE technique.

This study compared time for onset, duration of labour analgesia of first epidural dose of 0.125% Levobupivacaine and 0.2% Ropivacaine with fentanyl as epidural drug for labour analgesia using CSE technique and also, to assess quality of labour analgesia, maternal and foetal outcome, incidence instrumental delivery, and maternal satisfaction.

Material and Methods

Following approval from the ethical committee, this prospective, randomized double blinded study was carried out on 50 parturient from October 2017 to June 2019 in JSS Medical College. Total 50, 25 in each group, based on power of study 80% with alpha error of 5%. All parturient underwent a thorough pre-anaesthetic evaluation (PAE), and have been explained in detail about the methodology and advantage of CSE. Informed written consent was taken before institution of CSE.

All parturient requesting for labour analgesia; singleton pregnancy; vertex presentation; term gestation (36-42 weeks); parturient in labour with cervical dilation <4 cm were included in the study and Malpresentation, preterm labour, parturient with complications of pregnancy (gestational diabetes, pregnancy induced hypertension, antepartum haemorrhage), any foetal anomaly; consent refusal; contraindication for central neuraxial blockade were excluded from the study.

Parturient were randomly allocated into two equal groups by using SNOSE technique. (Serially numbered opaque sealed envelope) into *Group L*- Parturient receiving intermittent boluses of 10ml of epidural 0.125% Levobupivacaine with 2mcg/ml Fentanyl and *Group R*-Parturient receiving intermittent boluses of 10ml of epidural 0.2% Ropivacaine with 2mcg/ml Fentanyl.

Parturient were given intravenous (IV) Ringer Lactate at the dose of 10 ml/kg body weight. After connecting multiparameter monitor with ECG, Pulse

rate, $SP0_2$ probe, non-invasive blood pressure (NIBP), respiratory rate, baseline pain score, foetal heart rate and initial rate of oxytocin infusion readings were recorded just before the procedure. Emergency resuscitation instruments were kept ready. Parturient were placed in the right lateral position and, under aseptic precautions epidural catheter was introduced with 18 G Tuohy's needle using loss of resistance technique through midline approach at L2-L3 or L3-L4 Level, after negative aspiration for blood and cerebrospinal fluid, epidural catheter was placed 3-4 cm inside the epidural space. Spinal analgesia using 27 G Quincke's spinal needle with 0.5ml (2.5 mg) 0.5 % Bupivacaine Hyperbaric with 0.5 ml (25 mcg) of fentanyl was given to both the groups. Immediately after the procedure parturient were turned to supine position with a left uterine tilt. Parturient labour pain relief was assessed using visual analogue score (VAS) (0= no pain, 10= worst possible pain experienced). VAS score and haemodynamic status were recorded at the time of instituting analgesia (0 minutes) and then on at interval of 5 minutes till 20 minutes and further at half hourly interval till 90 minutes.

When the parturient experienced pain equivalent to VAS score of 4 after intrathecal analgesia, first 10 ml bolus of epidural 0.125% Levobupivacaine with 2 mcg/ml Fentanyl or 10 ml epidural 0.2% Ropivacaine with 2 mcg/ml fentanyl was given according to the groups. The time of giving the top up was considered as 0 minutes and the same parameters were measured at 0,5,10,15,45,75 and 90 minutes. Further top-ups were given on demand until full dilation of the cervix, after which no further top ups were given. The same protocol was followed till the foetus was delivered.

Level of sensory block was tested by pin prick method using a blunt tip 22 G needle. Development of motor blockade was assessed by modified Bromage scale (0=No impairment, 1= unable to raise extended legs able to move knee and feet, 2= unable to raise extended legs as well as flex knee able to move foot, 3= not able to flex ankle, feet or knees)

The mean onset of analgesia (from time of first bolus dose to time of achieving VAS ≤ 3), total duration of analgesia (the time interval between initiation of analgesia and patient developing pain after the first bolus, VAS>4).

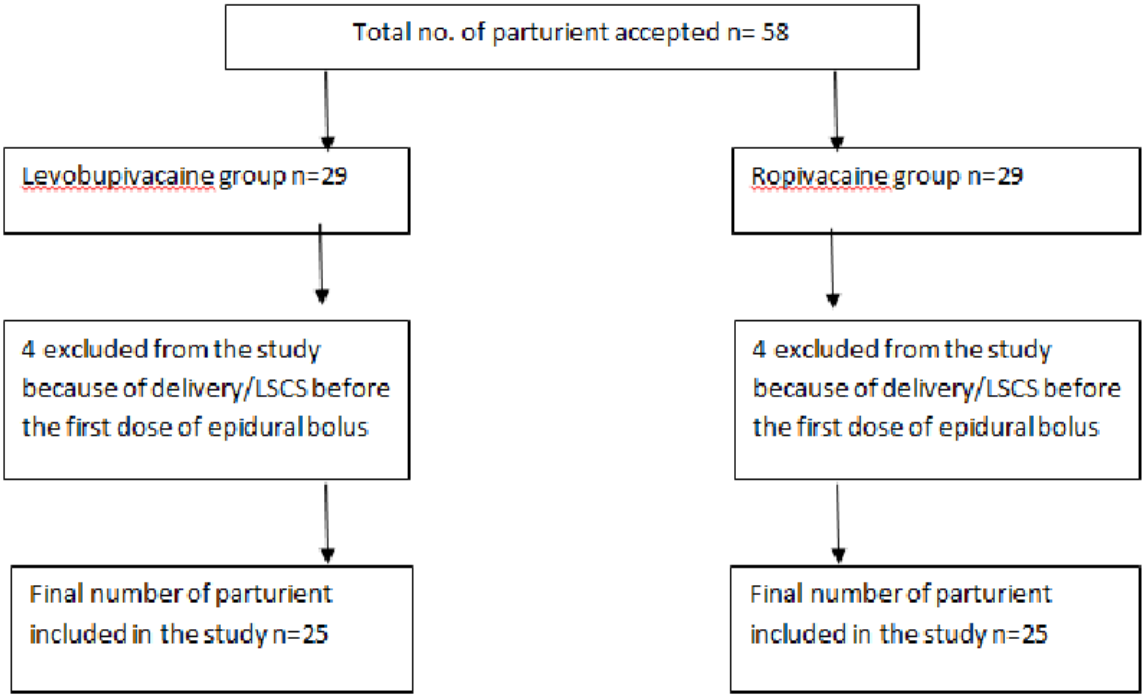
Haemodynamics (pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, saturation, and respiratory rate) of the parturient, mode of delivery, incidence of sensory and motor blockade, the APGAR scores of the neonate at 1 minute and 5minute were noted between two groups. The parturient was monitored for 2 hours following delivery and epidural catheter was removed. The parturient were followed up on the next day to enquire about their views on the procedure and their subjective assessment of satisfaction about the labour analgesia, based on satisfaction scale 1- No satisfaction, 2- Satisfaction,3- Good satisfaction, 4- Excellent satisfaction.

Any parturient who were taken up for caesarean section or delivered, either before the first dose of epidural or before 90 mins of administering the first bolus was excluded from the study.

Sample size was calculated to be 50 with 25 in each group [3], based on power of study 80% with alpha error of 5%.Data were analysed using SPSS version 24 (licensed to the institution). Demographic data were analysed using analysis of variance. Onset and duration of first dose of epidural analgesia were analysed with using unpaired t-test. Quality of analgesia, and foetal APGAR score assessed with Mann-Whitney U test. Hemodynamic parameters were assessed with Student's t test. Mode of delivery, instrumental among normal vaginal delivery and maternal satisfaction were assessed with percentage.

Data were expressed as Mean ± SD. Standard tests of significance were applied to determine the P value. P < 0.05 was considered significant and less than 0.001 as highly significant.

Observation and Results



Consort flow chart

Result

There were no significant differences between the two groups with respect to maternal demographic characteristics, parity, cervical dilatation, and weight of the patient.

Table 1: Demographic Data

Characteristics	Group R (n=25)	Group L (n=25)	p-value
Mean age (Years)	24.8800	26.4000	0.23
Mean weight (kg)	56.8800	57.8400	0.681
Cervical dilatation (cm)	3.4000	3.4800	0.64

Mean duration of spinal analgesia in Levobupivacaine Group L 107.9+/- 5.53 minutes whereas in Ropivacaine Group-R, it was 104.64 +/- 5.72 minutes, which was not significantly different. (p= 0.48)

Epidural Bolus

The mean onset of analgesia: From time of first bolus dose to time of achieving VAS ≤3 in pain score. Mean onset of analgesia in Levobupivacaine Group-L is 21.480+/- 1.32 min and in Ropivacaine Group-R is 16.280 +/- 1.59 min.(P=0.000).

The total duration of analgesia after first epidural bolus: the time interval between initiation of analgesia and patient developing pain after the first bolus VAS>4.

Mean duration of analgesia of first epidural dose in Levobupivacaine Group-L is 82.160 +/- 2.07 minutes and in Ropivacaine Group-R is 72.080 +/- 1.97 minutes, the difference in mean duration of analgesia was statistically significant. (P=0.000). [Table no 2].

Table 2: Onset and duration of first dose epidural analgesia

	Group L	Group R	
Mean onset of analgesia (min)	21.480±1.32	16.280±1.59	P= 0.000
Mean Duration of analgesia (min)	82.160 ± 2.07	72.080 ± 1.97	P= 0.000
Total mean duration of Labour analgesia (in min)	330.64±8.53	319.05±13.442	P=0.463

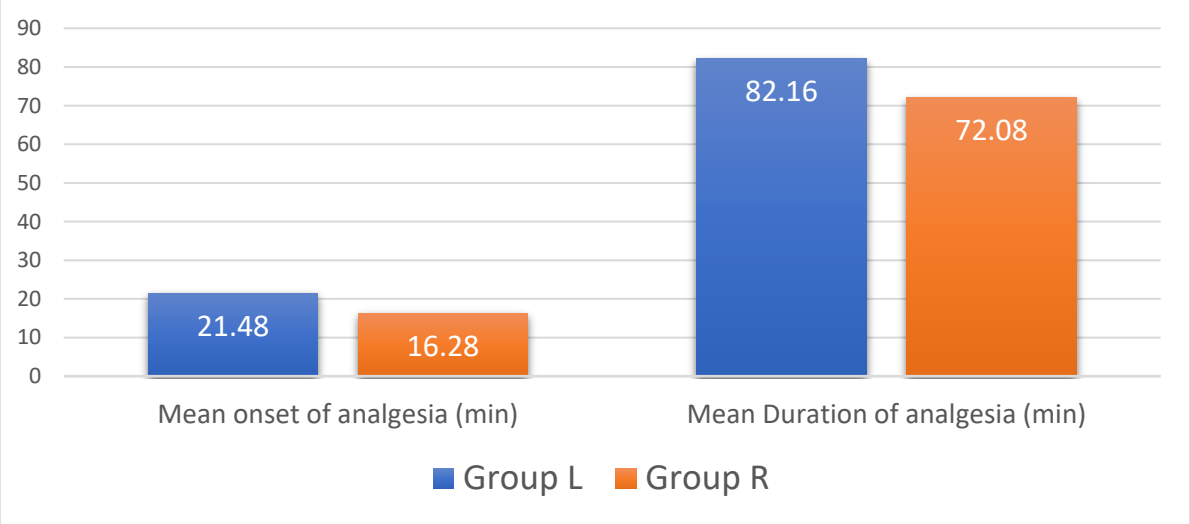


Figure 1: Onset and Duration of analgesia of first epidural bolus

Assessment of pain by visual analogue score

VAS score during the first and second stages of the labour were comparable without any significant statistical difference. [Table no. 3]

Table 3: Mean visual analogue scale scores

VAS score	Group R (n=25)	Group L (n=25)	p = 0.701 (for L-Group)
0-3	18 (72.0 %)	19 (76.0 %)	
4-5	7 (28 %)	4 (16 %)	p =0.736 (for R-Group)
6-7	0	2 (8%)	
8-10	0	0	

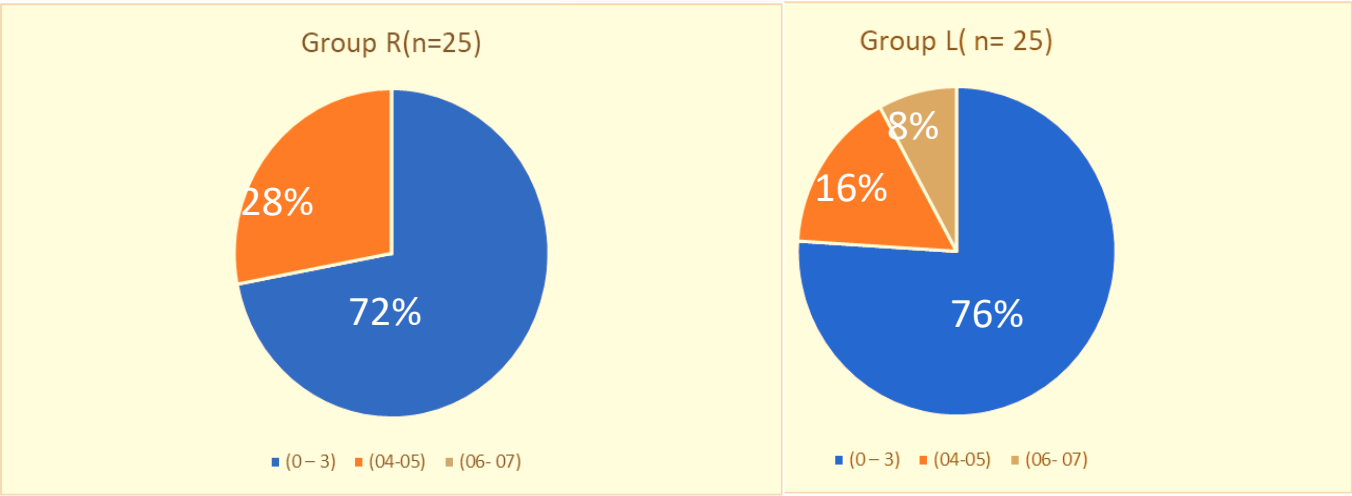


Figure 2: Assessment of Pain- Mean visual analogue scale scores

Mode of delivery: There was no significant difference between the groups regarding mode of delivery. In Group R there were 80% Vaginal deliveries, 8% LSCS, 12 % Instrumental deliveries. Whereas, Group L 68 % had Vaginal deliveries, 12% LSCS, 20% Instrumental deliveries. [Figure no. 2]

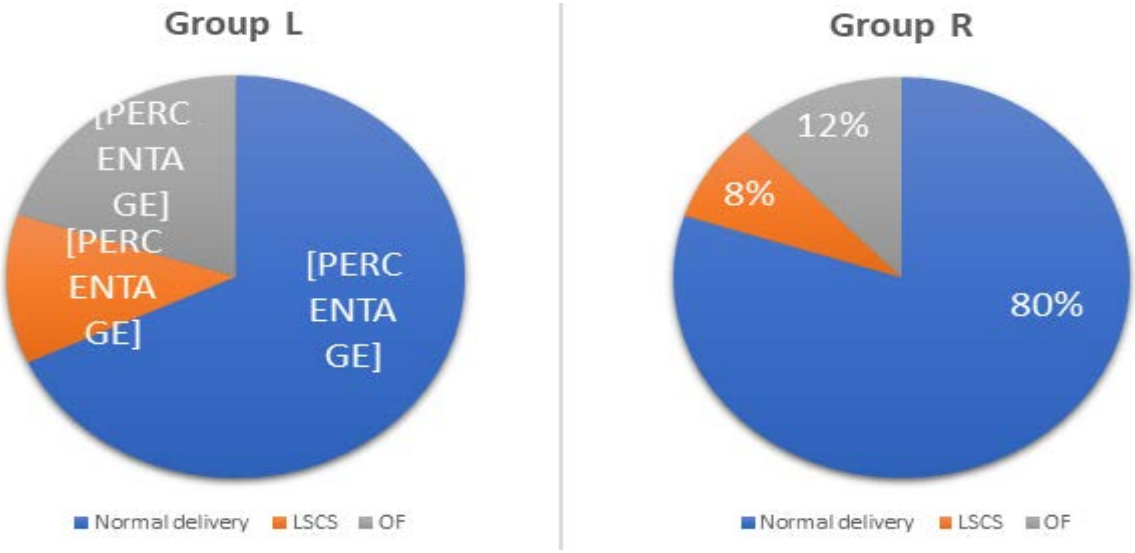


Figure 3: Mode of Delivery

Neonatal outcome

Neonatal outcome was assessed based on APGAR scores at the 1st and 5th minutes. There was no significant difference in APGAR scores between the groups at 1st min (p=0.469) and 5th min(p=0.128). None of the neonates had scores less than 7 at 1st min and 8 at 5th min.

There was no significant difference between the two groups with respect to maternal haemodynamic parameters after administering CSE. None of the parturient developed hypotension, bradycardia or desaturation after administering epidural top-up.

Maternal satisfaction was assessed based subjective assessment as excellent, good, satisfactory and not satisfactory. 96% parturient in Group-L experienced good satisfaction with CSE whereas in Group-R 92% parturient experienced good satisfaction with CSE. [Figure no 3]

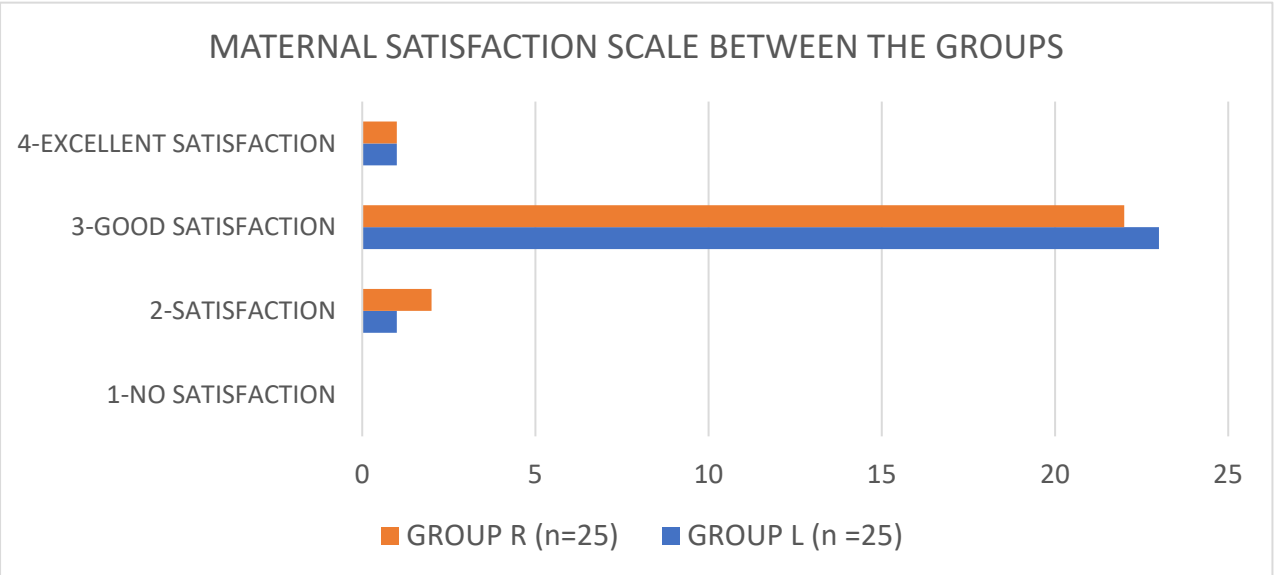


Figure 4: Satisfaction Scale

Discussion

Labour constitutes one of the most painful events experienced by women during their life time. "Painful labour may cause excessive maternal stress, increased oxygen demand, hyperventilation and results in increased stress hormone secretion leading to uterine vasoconstriction, increased uterine contractility, hypoperfusion of the fetoplacental unit, causing foetal hypoxia and acidosis" [3] .

This can be prevented by providing labour analgesia through various methods that are safe for mother and foetus. Combined spinal epidural (CSE) technique gained popularity because of fast onset of analgesia via intrathecal administration and maintenance through use of epidural catheter.

Simmons SW *et al* [4] studied CSE versus epidural analgesia in labour and proved that CSE was a better technique as it has faster onset of analgesia (mean difference (MD)-2.87 min; 95 % confident interval). Karadjova D *et al* [5] in their study found that CSE technique provides rapid onset labour analgesia with less motor blockade and they concluded that CSE is the technique of choice in multiparous patients.

Hence we selected CSE technique for our study with use of 0.5% Bupivacaine heavy 0.5 ml with fentanyl 25 mcg (0.5 ml) intrathecally which is the most common combination of drugs used for intrathecal administration in CSE technique for labour analgesia. For epidural, most commonly used drugs for labour analgesia are Bupivacaine, Levobupivacaine or Ropivacaine. Levobupivacaine is preferred over Bupivacaine because of its reduced cardiotoxicity as well as decreased intensity of motor blockade. Very few studies have compared Levobupivacaine and Ropivacaine for Labour analgesia.

Hence, we selected CSE technique using 0.125% Levobupivacaine and 0.2% Ropivacaine with fentanyl as epidural drugs for this study. This is a prospective, double-blinded, comparative study between the two drugs. The parameters such as onset and duration of first epidural bolus dose of the test drugs, quality of analgesia, maternal and foetal outcome, mode of delivery and maternal satisfaction were compared.

Onset and duration of intrathecal analgesia

In our study Intrathecal 2.5 mg Bupivacaine with 25 mcg fentanyl was used and mean duration of analgesia was 104.640 $\pm$5.72 min and 107.9$\pm$5.53 min in Group R and Group L respectively which was not statistically significant. (p=0.48).

Administration of drug through epidural catheter

Intermittent epidural top-up dose

In our study Intermittent bolus of 10ml of epidural 0.125% Levobupivacaine with 2mcg/ml fentanyl or 10 ml of epidural 0.2% Ropivacaine with 2mcg/ml fentanyl was given to parturient on demand. Iintermittent Epidural bolus technique has advantage of better spread of the LA in the epidural space with better analgesia. George *et al* in their study, found that intermittent bolus (IEB) for labour analgesia improves maternal satisfaction and reduce LA consumption, because of better spread of LA in epidural space. In their study compared intermittent bolus and continuous epidural infusion for labour analgesia and did not detect any significant difference between both groups, with respect to rate of CS & duration of labour. They concluded that IEB reduces LA consumption as the dose can be titrated according to the progression of labour, improving maternal satisfaction with less frequent motor blockade, breakthrough pain being the greatest disadvantage. Rani P *et al* [6] found that intermittent bolus method to be more efficacious in producing effective analgesia with low drug concentrations.

First epidural bolus- The mean onset of analgesia

In our study, the time for onset of analgesia after giving first epidural top-up was faster with Ropivacaine - 21.480±1.32 min in Group L and 16.280 ±1.59 min in Group R (p=0.000). This was statistically significant. The time of onset of analgesia was taken as the time of first bolus dose to time of achieving VAS≤3. Our study was comparable to Rani P *et al* [6], who observed an earlier onset of analgesia with Ropivacaine (21.43 ±2 min) as compared to Levobupivacaine (23.57 ±1.71 min) (p<0.05). In their study the concentration of both Levobupivacaine and Ropivacaine was 0.1 % compared to our study where we have used levobupivacaine 0.125 % and Ropivacaine 0.2 %, which is higher than their study. Hence the mean duration of onset of analgesia in both the groups is longer compared to our study. Chhetty YK *et al* [7] in their study found a faster onset of analgesia in Ropivacaine group. This was similar to our study, but with very rapid onset of analgesia (0-5 min) which could be because of the larger volume (15 ml) of drug used along with fentanyl 2 mcg/ml.

Duration of first bolus dose of epidural analgesia

The total duration of analgesia after first dose of epidural in our study was 82.160±2.07 minutes and 72.080 ±1.97 minutes in parturient given Levobupivacaine and Ropivacaine, respectively which was found to be statistically significant (p= 0.000). Total duration is the time interval between initiation of analgesia and patient developing pain after the first bolus (VAS>4). Total mean duration of labour analgesia in levobupivacaine and ropivacaine were 330.64±8.53 min and 319.05±13.44 min (p=0.463).

Rani P *et al* [6] in their study found that the duration of analgesia was shorter in Ropivacaine group (60 ± 14 min) than in Levobupivacaine group (68 + 11 min) (p=0.027), which was similar to our study. The duration of analgesia of the first bolus was less than our study of both levobupivacaine and Ropivacaine group, as the concentration of both the drugs used is less (0.1 %). Chhetty YK *et al* [7], in their study found a longer total duration of analgesia with 0.2 % Ropivacaine (132± 56.81 min), unlike in our study (Ropivacaine -72.080 ±1.97 minutes) as they had used larger volume (15ml) with fentanyl 0.2 mcg/ml.

In a study by Attri J *et al* [8], the duration of analgesia was found to be longer with Levobupivacaine compared to Ropivacaine - 117.00± 11.86 min with 0.125 % Levobupivacaine as compared to 90.17± 8.85 min with 0.2 % Ropivacaine, both with fentanyl 30 mcg (p<0.005). This was similar to our study but with longer duration of epidural analgesia because of higher volume (15 ml) of the drugs used in their study.

Effectiveness of analgesia

Pain is a subjective phenomenon, so pain reduction is difficult to measure. In our study pain relief was evaluated by using "Visual analogue scale (VAS) (0 to 10)".

In our study the pain score during the first and second stages of labour were comparable without any significant difference between the two groups (p> 0.05). 18 (72%) parturient had VAS score ≤3, and 7 (28 %) had VAS= 4-5 in Group R while, 19 (76%) had VAS score ≤3, 4(16%) had VAS= 4-5 and 2 (8%) had VAS= 6-8 in Group L. Similar to our study, Akkamahadevi *et al* [9] found that pain relief was excellent with comparable VAS scores, when using CSE technique. Bhagwat *et al* [10] found that all the parturient in CSE group had VAS score of zero at thirty minutes. In our study, we found similar results with parturient of both the groups having effective analgesia (VAS scores less than 3) after epidural boluses.

Mode of delivery

In our study there was no difference between the groups regarding mode of delivery. In Group R (n=25) had 20 (80%) vaginal deliveries, 2(8%) LSCS, 3(12 %) Instrumental deliveries. Whereas, Group L (n=25) had 17(68 %) Vaginal deliveries, 3(12%) LSCS, 5(20%) Instrumental deliveries.

Halpern SH *et al* [11] found no significant difference in any of the obstetrical outcomes- labour duration, second stage duration, mode of delivery (p= 0.12) (Ropivacaine vs Bupivacaine for labour) similar to our study.

Aneiros F *et al* [12] and Beilin Y *et al* [13] in their study found no difference in mode of delivery among primigravidae receiving epidural Bupivacaine or Ropivacaine or Levobupivacaine.

Singh SK *et al* [14], in their study found that CSE did not affect the delivery outcome, with similar CS (16 % vs 15 %, respectively in CSE & non- CSE group) and instrumental delivery rates (11% vs 16 %, respectively in CSE & non- CSE group). Norris MC *et al* [15] found that progress of labour and outcome was unaffected by CSE technique, when compared with traditional epidural. This was comparable to our study.

Cambic CR *et al* [16] in their meta-analysis found that effective neuraxial analgesia does not increase the CS rates.

Neonatal outcome

Neonatal outcome was assessed based on APGAR scores at the 1st and 5th minutes.

In our study, there was no difference in APGAR scores in both groups at 1st min (p=0.469) and 5th min (p=0.128). None of the neonates had scores less than 7 at 1 st min and 8 at 5th min.

Singh SK *et al* [14] in their study, found that neonatal outcome was unaffected by CSE technique. At 1 min 3 neonates (n=55) in CSE group had APGAR scores of less than 7, with a p value more than 0.05 showing it was statistically insignificant. None of the neonates had an APGAR score of less than 7 at 5 min. This was comparable to our study.

Beilin Y *et al* [13], in their study found no significant difference in neonatal outcome in primigravidae receiving epidural labour analgesia (Bupivacaine vs. Ropivacaine vs. Levobupivacaine). This finding was similar to ours.

Attri J *et al* [8], in their study found 1 baby had APGAR score 7 at 1 min with 0.125 % Levobupivacaine and 2 had a score of 7 at 1 min in 0.2 % Ropivacaine group and none had an APGAR <8 at 5 min (p>0.05). This was found to be similar to our study.

Incidence of motor block

Motor blockade was assessed using modified Bromage score (3- Unable to flex ankles, 2- Unable to flex knees, 1- inability to lift leg straight, 0-no motor weakness).

In our study, 13 out of 50 women experienced transient initial motor blockade (Bromage score 1) after giving intrathecal 0.5 ml 0.5% hyperbaric Bupivacaine with 25 mcg fentanyl, but none of them had any motor blockade beyond 30 minutes.

Y Lim *et al* [17] study found that most frequent incidence of lower limb motor block with intrathecal 2.5 mg Bupivacaine. 5 out of 20 parturient developed motor blockade (Bromage scale 1) which did not extend beyond 30 minutes. These results were similar to our study.

Haemodynamics

Monitoring of vitals (HR, blood pressure & SpO2) were done to assess the haemodynamic stability.

In our study there was no significant difference between the two groups with respect to baseline vitals. We found no significant difference between the two groups with respect to haemodynamic parameters after administering CSE. None of the parturient developed hypotension, bradycardia or desaturation after administering epidural top-up. Sethi S *et al* [8] and Rani P *et al* [6] in their study there

were no significant differences in haemodynamic parameter between groups.

Satisfaction scale

All the parturient in both the groups were satisfied with the quality of labour analgesia provided to them.

Akkamahadevi *et al* [9] in their study found that more than 90% of the parturient in both the groups were satisfied with the quality of labour analgesia. This was found to be similar to our study.

Complications

Brief episodes of pruritis, one of the most common side effects of intrathecal fentanyl, was reported among 18% and 17% of the women belonging to Groups R and L, respectively. It subsided own its own

Conclusion

In our study, comparison between intermittent epidural bolus of 0.125% Levobupivacaine with fentanyl and 0.2% Ropivacaine with fentanyl in labour analgesia using CSE technique was taken.

We found that Ropivacaine produces early onset analgesia than Levobupivacaine but Levobupivacaine had significant prolonged analgesia compared to Ropivacaine. Both the drugs are safe for the mother and neonate

Maternal satisfaction and foetal outcome were similar with the both drugs. There were no hemodynamic disturbances and no motor blockade noted. There was no difference in mode of delivery, caesarean section rate with the use of these drugs.

Recommendation

Alleviating pain and providing maternal comfort during labour are of paramount importance. Epidural analgesia is considered to be a proven technique for control of pain. There is no adverse maternal or foetal outcome because of the procedure alone. The use of ropivacaine and levobupivacaine, which are less cardiotoxic is highly recommended for administering labour analgesia.

Limitations

Instead of intermittent boluses alone, combination of continuous infusion in the form of programmed intermittent bolus or computer integrated PCEA can be used to achieve satisfactory conduct of labour analgesia. Sample size could have been greater than what we have concluded. Only parturient belonging to ASA PS- II were included in the study.

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