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Randomized Comparative Study to Evaluate the Effectiveness of Ropivacaine 0.125% Versus 0.2% with Fentanyl in Epidural Labor Analgesia

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Abstract: ***Background: Minimum effective concentration of local anesthetics for providing optimal labor epidural analgesia and the strategies aiming to reduce their consumption are continuously being searched. Objectives: The objective of this study was to evaluate the efficacy of 0.125% and 0.2% ropivacaine both mixed with fentanyl 2 mcg/ml for epidural labor analgesia. Materials and Methods: A total of 80 parturients in active labor were randomly assigned to two groups of 40 each, to receive an epidural injection of 15 ml ropivacaine 0.125% with fentanyl (2 mcg/ml) in group R1 and 15 ml of ropivacaine 0.2% with fentanyl (2 mcg/ml) in group R2 as initial bolus dose. Same dose regimen was used as subsequent top-up dose on patients demand for pain relief. The duration and quality of analgesia, motor block, top-up doses required consumption of ropivacaine and fentanyl and feto-maternal outcome in both groups were compared. Results: Effective labor analgesia with no motor blockade was observed in both groups with no failure rate. Onset of analgesia was significantly faster in group R2 (75% parturients in 0-5 min) as compared to group R1 (25% parturients in 0-5 min), P < 0.001. Duration of analgesia after initial bolus dose was also significantly longer in group R2 (132 ± 56.81 min) than in group R1 (72.25 ± 40.26 min), P < 0.001. Mean VAS scores were significantly less in group R2 than in group R1 at 5, 60, and 90 min, P < 0.01. Requirement of top-up doses was significantly less in group R2 (0.05 ± 0.22) as compared to group R1 (0.80 ± 0.65), P < 0.001. Consumption of ropivacaine was comparable in both the groups (33.75 ± 12.16 mg in group R1 and 31.50 ± 6.62 mg in group R2 P > 0.05), but consumption of fentanyl was significantly more in group R1 (54.00 ± 19.45) as compared to group R2 (31.50 ± 6.62), P < 0.001. There were no significant changes in hemodynamics, nor adverse effects related to neonatal or maternal outcomes in both groups. Conclusion: It was concluded that both the concentrations of ropivacaine (0.2% and 0.125%) with fentanyl are effective in producing epidural labor analgesia. However, 0.2% concentration was found superior in terms of faster onset, prolonged duration, lesser breakthrough pain requiring lesser top-ups, and hence a lesser consumption of opioids.***

Keywords: Epidural labor analgesia, labor analgesia, ropivacaine 0.2% versus 0.125%, fentanyl

1. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Among these labor is a very painful process. It represent the most common form of acute severe pain in adult life, the severity compared to that of causalgia, cancer pain and amputation of digit and expressed as worst pain experienced by the patient.

The pains of labor result in a maternal stress response, which is neither beneficial for the fetus nor the mother. Evidence is suggestive that labor disorders including maternal hypertension, dystocia, meconium staining, and fetal distress are stress related. Hence, maternal pain relief not only benefits the parturient, but her neonate also.

Of all the available methods of labor analgesia, epidural analgesia satisfies the basic requirements of labor analgesia by fulfilling the objective of decreasing the pains of labor without affecting other sensations such as a desire to push and to allow normal walking while preserving the tone of pelvic floor muscles as well as retaining the sensation of the baby's head in the vagina; thus, allowing labor to proceed unhindered.

Ropivacaine, an amide local anesthetic is less cardiotoxic in animals as well as it may also be more selective for sensory fibers when compared to other local anesthetics, producing less motor block.This allows for increased maternal ambulation and also allows for normal progression of labor, which translates into fewer instrumental deliveries and more vaginal deliveries although this is controversial. These factors suggest that ropivacaine may be superior to bupivacaine in obstetric analgesia.

Minimum local anesthetic concentration (MLAC) studies by up and down sequential allocation have found both 0.2% and 0.1% ropivacaine to be effective for labor analgesia. OPRM A118G gene has been reported to be present in a higher number of Asians as compared to their Western counterparts, which pre- disposes the Asian populace to a higher degree of pain perception.

Studies are lacking , which highlight the efficacy of 0.2% versus 0.125% ropivacaine for labor analgesia, which prompted to undertake this study.

The objective of this study was to evaluate 0.125% versus 0.2% ropivacaine, with 2 µg/ml of fentanyl in epidural labor analgesia, regarding their sensory and motor block characteristics as well as the fetomaternal outcomes.

2. Materials and Methods

After approval of the Institutional Ethical Committee, this prospective randomized double-blinded study was conducted on 80 term parturients of American Society of Anesthesiologists (ASA) grade I and II having uncomplicated pregnancy in a vertex presentation.

Patient selection:
Parturients in active labor, having contractions at least once every 5 min, not having any contraindication to epidural analgesia, and who requested epidural analgesia for pain relief were enrolled in this study.

Inclusion Criteria:
Only those parturients who fulfilled the following criteria will be chosen for the study

1) The mothers of booked cases, had under gone routine antenatal checkups and all antenatal investigations should be within normal limits.
2) Aged 18 years or above and should be more than 150 cm tall.
3) Either prime or gravid two.
4) The presentation singleton, term foetus with vertex presentation.
5) Inactive labour with a cervical dilatation between 4-6cm

Exclusion Criteria :

1) Patient refusal
2) Hypersensitivity to study drugs
3) Bleeding disorders
4) Decreased platelet counts
5) Sepsis
6) The mothers having co-existing diseases like diabetes, pregnancy induced hypertension, bronchial asthma, epilepsy, ischaemic or valvular heart disease or previous Caesarean section.
7) History of drug abuse
8) Spinal column deformities and spine surgery.

Sample size and group allocation:
Expecting ropivacaine (0.2% vs. 0.125%) + fentanyl 2 μg/ml to decrease visual analog scale (VAS) scores to <3 values, a power analysis resulted in a calculated sample size of a minimum of 28 subjects per group to obtain statistical significance assuming and α error of 0.05 and power of 0.9.

The study was designed to provide 90% power to detect a decrease in success rate from 90% to 70% with a one-tailed test at 5% significance level.

However, since a minimum of 30 subjects are required for a clinical study to be valid and to compensate for dropouts a sample size of 40 subjects per group was chosen.

Study patients (n = 80) were randomly assigned to one of two groups of 40 each, using a computer generated table of random number to receive epidural injection using either, 15 ml of ropivacaine 0.125% with 2 μg/ml fentanyl (group R1) or 15 ml of ropivacaine 0.2% with 2 μg/ml fentanyl (group R2).

For group R1, 15 ml of 0.125% ropivacaine was prepared by taking 2.5 ml of 0.75% isobaric ropivacaine and diluting it with 12.5 ml of 0.9% normal saline.

For group R2, 15 ml of ropivacaine (0.2%) was taken directly from a 20 ml ampoule (Ropin, Neon). 30 μg of fentanyl were taken by using six parts from a tuberculin syringe graduated in markings to divide 1 ml (50 mcg/ml) into 10 parts and added to 15 ml of ropivacaine in both groups to achieve a final concentration of fentanyl (2 mcg/ml).

Double blindness of the study was ensured by involving, three different anesthesiologists for preparing the drugs, administering them and for recording the data.

Performing Block:
After informed consent patients were subjected to a thorough pre- anesthetic evaluation. Before placement of the epidural catheter, VAS score was noted with VAS 0 = no pain and 10 = the worst imaginable pain along with baseline vitals. After starting a 500 ml infusion of Ringers' lactate in an 18G peripheral intravenous canula, parturients in both groups were placed in the left lateral position.

Following strict aseptic techniques, and infiltrating 2% lignocaine HCl into the intervertebral space, epidural space was identified at L3-4 or L4-5 space using a loss of resistance technique to normal saline with an 18G Tuohy needle and an 18-gauge multi-orifice catheter was threaded through the cephalad directed tip of the epidural needle to a depth of 5 cm into the epidural space.

If there was no blood or cerebro spinal fluid (CSF) on aspiration from the epidural catheter, depending on the group allocated, a 3-ml test dose of the study medication was administered through the catheter.

The presence of clinical signs of an intravascular injection were sought, for the following 2-3 min, by asking the patient whether she felt dizzy, had tinnitus, or a metallic taste in her mouth.

If there were no signs of an intravascular injection, the catheter was secured and the woman was placed in the supine position with left uterine displacement.

Five minutes after the test dose, if there were no clinical signs of subarachnoid injection (as evidenced by the patient's ability to move her legs and the absence of hypotension), an additional 12 ml of the study solution was administered.

This dose was defined as first initial bolus dose and time was noted. The adequacy of analgesia was assessed 5 min after the first initial bolus dose of study drug had been administered. Analgesia was considered adequate if pain score was <3.

Onset of analgesia was defined as from time of first bolus dose to time of achieving VAS <3. If analgesia was not adequate 15 min after the first initial dose, an additional 15 ml of study medication (second initial dose) was administered, and analgesia reassessed in the same manner. If pain relief

was inadequate at the peak of a contraction, 15 min after the second initial dose of ropivacaine; the epidural anaesthetic was classified as ropivacaine failure, and patient withdrawn from the study.

Presence of motor block in the lower extremities was assessed using a Breen modified Bromage scale (BMBS: Grade 1 as complete motor block to Grade 6 as no motor block). VAS and BMBS was assessed every 15 min.

All parturients were given a trial walk to assess their ability to ambulate.

An additional dose of ropivacaine 15 ml was given as a top-up dose on patient request, with a minimum gap of 15 min between two subsequent top-up doses. Epidural analgesia was continued through the second stage of labor.

At any point of time during the study period hypotension was defined as systolic blood pressure of <90 mmHg and was treated with bolus of 6 mg ephedrine HCl. Bradycardia was defined as heart rate < 60 bpm and was treated with bolus doses of 0.4 mg atropine sulfate.

Data recording:

Demographic data (age, weight, height), obstetric data (parity, dilatation of the cervix [0-10 cm], station of the vertex of the presenting part [−3 to +3], effacement of the cervix (%), membrane status were noted prior to the initiation of labor analgesia.

Pain score (VAS), sensory and motor block characteristics and vital parameters (pulse, mean arterial pressure, respiratory rate) were recorded at 0 (before epidural), 5, 15 min and then every 15 min till 1 h and then every 30 min until the delivery.

Sensory block height was assessed by loss of sensation to pin prick (blunt head of a pin). Onset of analgesia was defined as duration from injection of first initial epidural bolus dose to attainment of VAS <3 and duration of analgesia of initial bolus dose was defined as time of administration of study drug until the time of demand of top-up for the first time.

Motor block assessment was carried out by BMBS,[1-6] Romberg's sign, straight leg raising test, rectus abdominalis muscle test, and trial walk.

The time taken by the parturient to request for subsequent top-up dose was recorded. Labor was managed according to our obstetric department's protocols and mode of delivery (normal/ instrumental delivery/caesarean delivery) was noted.

Injection delivery interval was defined as the time from administration of first initial epidural dose until the delivery. Fetal heart rate was monitored throughout the study by using a cardiotocograph, and any evidence of fetal heart rate decelerations was recorded. Neonatal assessment was performed by assessing the Apgar score at 1 and 5 min.

Quality of maternal expulsive efforts was assessed by an obstetrician as Grade 0 – Failure, 1 – Incomplete, 2 – Good, 3 – Excellent.

Quality of analgesia was assessed by anesthesiologist as Grade 0 – Failure, 1 – Incomplete, 2 – Good, 3 – Excellent, 4 – Not possible to evaluate (NPE) if delivered by cesarean section.

Side-effects including nausea, vomiting, hypotension, hypersensitive reaction, shivering, fever, drowsiness, pruritus, respiratory depression, retention of urine, and weakness in limbs were noted.

Statistical analysis:
For categorical variables (presented as number [proportions]), the proportions of variances in the two groups were compared using the Chi-squared test with calculation of the X 2 statistic value and P value.

For quantitative variables (data presented as mean ± standard deviation [SD] measurements), the groups were compared using Student's t-test for independent samples.

For all statistical analyses, the level of significance was $P < 0.05$ and the software used was Microsoft Excel 2007 and Statistical Package for the Social Sciences.

3. Discussion

The ideal labour analgesic technique should be effective, safe for mother and foetus, should be easy to administer, should provide consistent, predictable and rapid onset of analgesia in all stages of labour, should be devoid of motor blockade and should preserve the stimulus for expulsive efforts during the second stage of labour.

Labour pain is a subjective experience with sensory and emotional components. Thus the perception of pain and response to it, varies from one parturient to the other.

Lumbar epidural technique as a means of obstetric pain relief has established its supremacy. Epidural analgesia is used principally for pain relief during labour. It is estimated that some 20% of all the parturients now receive epidural analgesia for pain relief in labour.

Safe and effective relief of pain during labour and delivery accomplished by the skillful use of epidural analgesia prevents the stress response in the mother. Maternal hypoxemia, hypocapnia, catecholamine secretion leading to uterine hypoperfusion, foetal hypoxia and acidosis are avoided.

Obstetricians and Anaesthesiologists have always feared that incidence of instrumental deliveries in women receiving epidural analgesia could be higher than in those who do not receive it.

Studies have revealed that the threshold of the obstetricians to perform assisted delivery is definitely lower when epidural analgesia is already present Ideally pain relief with regional techniques should be produced with the minimum disturbance to the progress of labour or to sympathetic func-

tions, sensory functions (proprioception) and motor functions of CNS.

Thus it is intriguing to the obstetric anaesthetist to strike a balance between patient satisfaction by providing good analgesia, reduces motor block thus making the parturient participate in labour and decrease instrumental deliveries due to prolonged second stage.

Previously, the local anaesthetics bupivacaine, lidocaine and 2-chloroprocaine were used to provide epidural labour analgesia.

Administration of local anaesthetics was by intermittent boluses or continuous infusions set at predetermined rates. However, some of the patients studied received larger doses of local anaesthetic than was needed for maternal comfort. More local anaesthetic can produce more motor and sympathetic blockade.

Impairment of uterine blood flow during labour is an important cause for foetal asphyxia and neonatal morbidity.

The last few years have been marked by the arrival of new local anesthetics; ropivacaine and levobupivacaine, with reduced systemic toxicity and a better preservation of motor function.

Toxicity is not an issue when low concentrations of local anesthetics are used as is the case in modern neuraxial labor analgesia. It seems evident that the adequate dilution of local anesthetics and the strategies aiming to reduce their consumption are more important than the choice of the local anesthetic by itself when the goal is to provide optimal neuraxial labor analgesia.

There are controversial data regarding minimum effective concentration of ropivacaine for initiation of epidural labor analgesia.

Using up and down sequential allocation MLAC of ropivacaine for epidural labor analgesia was reported to be 0.111% w/v (95% confidence interval [CI], 0.100-0.112).

In another study MLAC of ropivacaine alone was 0.13% (95% CI, 0.12- 0.13) compared to 0.09% (95% CI, 0.08-0.1) with sufentanil, $P < 0.01.46$ On the other hand, many authors found that ropivacaine 0.2% offers adequate analgesia more often than either 0.15% or 0.1% and the resultant motor blocks and hemodynamic effects are minimal.

Addition of fentanyl 2 mcg/ml to 0.1% ropivacaine improved analgesia to a quality similar to 0.2% ropivacaine.

In the present study, epidural labor analgesia with ropivacaine 0.125% or 0.2% both combined with fentanyl (2 mcg/ml) produced adequate labor analgesia in all the 80 parturients in both groups showing a 100% success rate of both concentrations.

However, observed that the onset of analgesia was significantly faster when labor analgesia was initiated with 0.2% ropivacaine as reported earlier that a decrease in time for onset occurs with increasing concentrations of epidural bupivacaine.In contrast, no difference in the onset of analgesia with increasing concentration of ropivacaine had also been reported.

Duration of analgesia of initial bolus dose was also significantly more with 0.2% ropivacaine in our study as observed by others.Addition of adjuvant opioids leads to further increase in duration of analgesia.

Time of first top-up was also significantly more in 0.2% group, which is in concordance to other studies.

Requirement of top-up doses was also significantly less frequent in 0.2% group, but total dose of ropivacaine was comparable in two groups (31.75 mg in group R2 and 33.75 mg in group R1) because repeated top-ups of 0.125% ropivacaine resulted in same total dose of ropivacaine.

Nevertheless repeated top-up doses had 2 mcg/ml fentanyl and led to consumption of significantly higher amount of fentanyl in group R1 (54 mcg in group R1 vs. 31.50 mcg in group R 2).

The recent trend in practitioners of labor analgesia is to use the least possible concentration of local anesthetic and adjuvant for the purpose of attaining analgesia.

The main undesirable side-effects with ropivacaine analgesia are hypotension, bradycardia, nausea, paresthesia, and urinary retention, which are considered mild and transient.

However, the side-effects observed with opioids are multivariate (nausea, pruritus, respiratory depression, lower Apgar scores in the neonate).

All of these undesirable effects warrant a decrease in the dosage of epidural opioids that are used for analgesia in the laboring patient.

The amount of ropivacaine and fentanyl that were required to attain analgesia in this study were comparatively high.

This could be attributed to the differences in the techniques of administering analgesia: Intermittent boluses versus infusion by patient controlled epidural analgesia (PCEA).

Studies have demonstrated that PCEA labor analgesia consumes significantly lesser amount of the local anesthetic opioid mixture.

In the present study, no motor block was observed in both groups, which is in concordance to others.

However, higher incidence of motor block in previous studies could be attributed to higher concentrations of ropivacaine (0.25%, 0.275%58,0.5%).

In a Cochrane systematic review of epidural versus no analgesic in labor that included 38 studies involving 9658 women; 13 of the studies reported hypotension as an adverse effect; also observed slight fall in the MAP and heart rate, but

none of the patients had episodes of hypotension and bradycardia requiring treatment as was also noted earlier that changes in maternal pulse rate (PR) and blood pressure are not related to Change in the dose of local anaesthetic. Injection delivery interval was comparable in both groups, but it was shorter as compared to others.

The reason for this difference is probably because other studies included only nulliparous parturients, whereas in this both nullipara and multipara parturients and a significant correlation between parity and duration of labor has been found in earlier studies.

In this study, maternal expulsive effort, instrumental delivery, and neonatal status were comparable in both groups as observed by others.

Authors of the Cochrane systematic review (2011) opined that epidural analgesia appeared to be effective in reducing pain during labor. However, women who used this form of pain relief were at increased risk of having an instrumental delivery.

Epidural analgesia had no statistically significant impact on the risk of cesarean section, maternal satisfaction with pain relief and long-term backache and did not appear to have an immediate effect on neonatal status as determined by Apgar scores.

However, they also stated that further research would be helpful to evaluate rare but potentially severe adverse effects of epidural analgesia on women in labor and long-term neonatal outcomes. this study was not designed with the objective of assessing the mode of delivery of the parturients participating in the study. Hence, appropriately powered and designed studies may help in further researching this aspect of labor analgesia.

No parturient had hypotension, hypersensitivity reaction, pruritus, nausea, urinary retention, vomiting, respiratory depression, weakness in the limbs or shivering, though cases of pruritus, hypotension, have been reported with epidural labor analgesia.

Both concentrations produced maternal expulsive efforts, parturient and anesthesiologist acceptance grades in excellent or good range similar to Beilin (92% satisfaction) and Leewho reported a satisfaction grade of 8 on a scale of 10 for all concentrations.

However, in this study parturient and anesthesiologist acceptance was significantly superior in R2 group, which could be attributable to less breakthrough pain that caused significantly less number of top-up requirement and VAS also remained significantly low at various time intervals.

The limitations of this study could be a requirement of a larger sample size which would give a wider perspective on maternal and neonatal side-effects. Similarly, a comparison of intermittent boluses versus a continuous infusion technique would give a better estimation of local anesthetic and opioid consumption in both groups.

4. Conclusion

In spite of the above limitations, arrived at the conclusion that both the concentrations are effective in producing labor analgesia.

Group R2 (0.2% ropivacaine) parturients; however, had a faster onset and significantly longer duration of analgesia with a single dose and required lesser top-ups, resulting in a significantly reduced consumption of opioids.

Hence, this study favors, the use of 15 ml of 0.2% ropivacaine with 2 mcg/ml fentanyl over 0.125% ropivacaine for labor analgesia.

It would be further interesting to evaluate the effect of varying the dose of administered drugs according to the stages and intensity of labor, which could further regulate the requirement of drugs and provide more effective analgesia.

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