Original Article

Epidural levobupivacaine versus a combination of levobupivacaine and dexamethasone in patients receiving epidural analgesia

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Abstract

Background and Aims: The use of dexamethasone as an adjuvant to local anesthetic rarely has been described. Some studies have demonstrated the analgesic effect of local spinal and systemic corticosteroids in combination with bupivacaine. It works by decreasing inflammation and blocking transmission of nociceptive C-fibers and by stopping the ectopic discharge of the nerve. The aim of this randomized controlled trial was to compare the efficacy of epidural levobupivacaine alone versus a combination of levobupivacaine with dexamethasone for labor analgesia.

Material and Methods: This prospective double-blind trial included the 60 primigravidas during vaginal delivery with a cervical dilatation ≥4 cm and 50% effacement randomly assigned to one of two groups – Group A (n=30): epidural levobupivacaine 0.125% in normal saline in a total volume of 15 mL and Group B (n=30): epidural levobupivacaine 0.125% in normal saline combined with dexamethasone 4 mg in a total volume of 15 mL. At first request of analgesia, 10 mL of 0.125% levobupivacaine was administrated through epidural catheter. Further analgesia was provided with 8 mL of 0.125% levobupivacaine hourly. Primary outcome measure was the duration of epidural analgesia. Secondary outcome measures include pain score by Visual Analog Scale score before the block and 15 min following it, the total amount of levobupivacaine used, Apgar score and umbilical vein blood gas analysis, maternal satisfaction, and side effects recorded.

Results and Conclusion: The duration of epidural analgesia was significantly longer ($P < 0.05$) upon adding dexamethasone to levobupivacaine. Total epidural levobupivacaine consumption was significantly lower ($P = 0.05$) in Group B. There were no statistical differences between the two groups regarding hemodynamics, pain score, neonatal outcome, and complications. Epidural dexamethasone plus levobupivacaine prolongs the duration of epidural analgesia during management of labor pain with hemodynamic stability and limited maternal and neonatal adverse effects.

Keywords: Dexamethasone, epidural analgesia, levobupivacaine

Background

The quality of labor pain has improved significantly with increased knowledge of physiology and pharmacotherapy of pain and development of obstetric anesthesia as a subspeciality.[1] Epidural labor analgesia results in adequate pain relief without affecting the course or duration of labor.[2] The quest for newer and safer anesthetic agents has always been one of the primary aims in obstetric anesthesia practice. There had been many modifications over the past two decades in regional anesthesia techniques, with the advent of several newer and safer local anesthetic agents. Bupivacaine is the most frequently used local anesthetic in regional anesthesia, being available in a commercial preparation as a racemic

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mixture (50:50) having two enantiomers, levobupivacaine, S (−) isomer, and dextrobupivacaine, R (+) isomer. Several studies reported serious central nervous system (CNS) and cardiovascular adverse reactions after intravascular injection or intravenous regional anesthesia; these incidences have been explained by the presence of R (+) isomer of bupivacaine. It has been shown that a safer pharmacological profile[3] with less cardiac and neurotoxic adverse effects was witnessed with levorotatory isomers.[4] Some studies reported the effects of corticosteroids in quality and quantity of sensory block in peripheral nerves.[5] Dexamethasone works by decreasing inflammation and blocking transmission of nociceptive C-fibers and by stopping the ectopic discharge of the nerve.[6] It has been shown that when dexamethasone was given as an adjunct for peripheral nerve blocks, the duration of postoperative analgesia was prolonged.[7] Recent studies did not report any complications associated with dexamethasone injection.[8,9] The aim of this randomized controlled trial was to compare the efficacy of epidural levobupivacaine alone versus a combination of levobupivacaine with dexamethasone for labor analgesia.

Material and Methods

This prospective double-blinded trial included 60 primigravidae after approval of research ethics committee. All participants between 18 and 35 years of age scheduled for normal vaginal delivery, American Society of Anesthesiologists (ASA) class 1 or 2 with no contraindication to regional anesthesia, and provided informed consent were involved in the study. Patient refusal was the main cause of exclusion upon enrollment. After enrollment and during the course of labor patients with failed epidurals, fetal distress and those who turned into CS were also excluded. Upon inclusion, a venous line was inserted and 15 mL/kg lactated ringer was given as a co-load. Noninvasive blood pressure, pulse oximetry, electrocardiography, and cardiotocography (CTG) were used for monitoring. Under complete aseptic conditions and through a midline approach, skin infiltration with 2% xylocaine was done and epidural block performed with the patient in the sitting position using a 17G Tuohy needle (Perifix®, Braun, Germany), at L2/3 or L3/4 intervertebral space with loss-of-resistance to air technique. Through the needle, a 19G epidural catheter was inserted and aspirated to detect blood or cerebrospinal fluid. Patients were then allocated randomly using a closed envelope technique into one of two groups: Group A: epidural levobupivacaine 0.125% (Chirocaine) in normal saline in a total volume of 15 mL (n = 30) and Group B: epidural levobupivacaine 0.125% (Chirocaine) in normal saline combined with dexamethasone 4 mg in a total volume of 15 mL (n = 30). An anesthesiologist not involved in the study prepared drug syringes. After epidural injection, women were turned to supine position with left lateral displacement of the uterus to prevent aortocaval compression. Afterward, the main primary outcome measure was the duration of analgesia; upon reappearance of pain, 8 mL of 0.125% levobupivacaine was given through epidural catheter. Further analgesia was provided with 8 mL of 0.125% levobupivacaine hourly. All women were followed up until delivery on a partogram with assessment of pain and hemodynamics. Secondary outcome measures were pain assessment using Visual Analog Scale (VAS) (0 = no pain and 10 = worst possible pain) at baseline before the block and 15 min after the block, total levobupivacaine used, neonatal outcome (Apgar score at 1 and 5 min and umbilical vein blood gas analysis), side effects, and maternal satisfaction score (0 = poor, 1 = fair, 2 = good, and 3 = excellent). Decrease in mean arterial blood pressure >25% from baseline or heart rate <60 was treated with ephedrine 10 mg iv boluses or atropine 0.6 mg increments subsequently. Fetal heart rate pattern was regularly monitored by obstetrician and managed accordingly.

Sample size calculations were performed for unpaired t-test for independent samples with time to analgesic supplementation in the two groups as the primary outcome variable in this study. Previous studies showed that standard deviation of time for analgesic supplementation in levobupivacaine + dexamethasone group was about 7.8 h, with a mean of 13 h[10] and standard deviation of time for analgesic supplementation was 4.8 h, with a mean of 6.1 h in levobupivacaine group.[10] Taking power 0.9 and alpha error 0.05, a minimum sample size of 30 patients was calculated for each group. A total of 40 patients were included in each group to compensate for possible dropouts.

Statistical analysis was performed using IBM SPSS Advanced Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample t-test or Mann–Whitney test. $P < 0.05$ was considered statistically significant.

Results and Conclusions

Sixty patients were included in this study. There was no remarkable difference among the two studied groups with regard to patients' age or gestational age, as well as body mass index, cervical dilation before analgesia, and cervical effacement. The mean duration of analgesia was statistically higher in levobupivacaine 0.125% with dexamethasone 4 mg compared with levobupivacaine 0.125% group, with values (81.57 ± 14.41) and

(63.77 ± 12.88), respectively ($P < 0.05$). The total amount of levobupivacaine requirement was statistically lower ($P < 0.05$) in levobupivacaine 0.125% with dexamethasone 4 mg compared with levobupivacaine 0.125% group, with values (94.2 ± 32.27) and (130.3 ± 42.8), respectively ($P < 0.05$). VAS after the block was statistically lower ($P < 0.05$) in levobupivacaine 0.125% group and in levobupivacaine 0.125% with dexamethasone 4 mg compared with VAS before the block. There were no statistically significant differences between the two groups with regard to the maternal and neonatal outcomes [Table 1]. The mean time of onset of sensory block at level T10 was statistically higher ($P < 0.05$) in levobupivacaine 0.125% with dexamethasone 4 mg compared with levobupivacaine 0.125% group, with values (12.8 ± 2.26) and (10.8 ± 2.87), respectively ($P < 0.05$). The mean time of high sensory block was statistically higher ($P < 0.05$) in levobupivacaine 0.125% with dexamethasone 4 mg compared with levobupivacaine 0.125% group, with values (17.4 ± 1.3) and (16.1 ± 1.54), respectively ($P < 0.05$). There were no statistically significant differences between levobupivacaine 0.125% group and levobupivacaine 0.125% with dexamethasone 4 mg, in level of high sensory block and no incidence of motor block are detected between two groups [Table 2]. There were no statistically significant differences among the two studied groups with regard to intrapartum mean arterial blood pressure, heart rate, and oxygen saturation. There were no statistically significant differences among the two studied groups with regard to neonatal outcome, patient's satisfaction, and complications in form of nausea, vomiting, and shivering [Tables 1 and 3].

Table 1: Demographic and clinical characteristics, analgesic profile, VAS, neonatal outcome, and maternal satisfaction

	Group A	Group B	*P*
Age (years)	26±4.8	27.1±4.8	0.1
BMI (kg/m^2)	24.3±2.3	24±1.9	0.3
Gestational age (weeks)	39±0.9	38.8±0.9	0.15
Cervical dilation before analgesia (cm)	4.57±0.8	4.7±0.8	0.58
Duration of analgesia (min)	63.8±12.9	81.6±14.4*	<0.001
Total amount of levobupivacaine (mg)	130.3±42.8	94.2±32.3†	0.0002
VAS			
Before the block	7 (6-9)	7 (6-9)	0.10
After the block	2 (0-2)*	2 (0-2)	0.22
Umbilical vein values			
PH	7.41±0.05	7.39±0.06	0.1
Apgar score			
After 1 min (min)	8 (6-8)	8 (6-8)	0.39
After 5 min (min)	10 (6-10)	10 (6-10)	0.28
Patient satisfaction	25 (83.3%)	24 (80.0%)	0.2

VAS=Visual Analog Scale; BMI=Body mass index. Group A=Levobupivacaine 0.125%. Group B=Levobupivacaine 0.125% with dexamethasone 4 mg. Data represented as [(mean±SD)], [no. (%)] or [median (range)]

Table 2: Characteristics of sensory

	Group A	Group B	*P*
Time of onset of sensory block at level T10 (min)	10.8±2.9	12.8±2.3*	0.002
Level of high sensory block	10 (6-12)	10 (6-12)	0.33
Time of high sensory (min)	16.1±1.54	17.4±1.3*	0.0004

*Group A=Levobupivacaine 0.125%. Group B=Levobupivacaine 0.125% with dexamethasone 4 mg. Data represented as [mean±SD)]. *Statistically significant higher compared with levobupivacaine Group A (P<0.05)*

Table 3: Frequency of intrapartum complications

	Group A	Group B	*P*
Nausea	4 (13.3%)	4 (13.3%)	0.5
Vomiting	2 (6.7%)	1 (3.3%)	0.25
Shivering	5 (16.7%)	2 (6.7%)	0.1

Group A=Levobupivacaine 0.125%. Group B=Levobupivacaine 0.125% with dexamethasone 4 mg. Data represented as [no. of patients (%)]

Discussion

The main finding of this prospective, double-blind randomized study was that addition of epidural dexamethasone to levobupivacaine offered a safe and effective method for prolongation of labor epidural analgesia together with reduction in the total required volume of levobupivacaine that can provide good maternal satisfaction with insignificant need for instrumental delivery, cesarean sections, and minimal side effects. The use of corticosteroids as an adjuvant to local anaesthetic rarely has been described. Prolonging the surgical anesthesia and analgesia can be achieved by increasing the duration of local anesthetic action which is often desirable. To prolong regional blockade, several additives have been used such as opioids, clonidine, and verapamil, but the results have been either inconclusive or associated with side effects.[11-13] It has also been described that corticosteroids were used as an adjuvant. The analgesic effect of local spinal and systemic corticosteroids combined with bupivacaine has been introduced by some studies.[14]

The mechanism of the pain relief done by corticosteroids is not quite comprehended. Injecting steroids perineurally is reported to affect postoperative analgesia. They alleviate the pain by decreasing inflammation and block transmission of nociceptive C-fibers and by stopping ectopic discharge of the nerves affecting only the C-fibers not the B ones.[15] Since this effect is reversible hence it is possible that steroids possibly have a direct action on cell membrane. Steroids could cause this effect by changing potassium channels' function in excitable cells.[16] Concerning the steroids' traditional theory, it states that they bind intracellularly to receptors and alter nuclear transcription. The optimum dose of epidural dexamethasone for postoperative analgesia has not been yet evaluated. The exact dose of dexamethasone added to

local anesthetics has not yet been described; the dose used in this study which is 4 and 8 mg was chosen as it seems to be safe in adults. The finding of this study supported idea of using dexamethasone in low doses as an adjuvant to local anesthetic can prolong the duration of pain relief. These results coincide with the findings of Khafagy *et al.*, who studied dexamethasone versus fentanyl concerning their efficacy when used epidurally, on postoperative pain relief. The study was performed on 90 patients ASA 1-2 undergoing lower abdominal surgeries, given either 50 μg fentanyl in group BF or 4 mg dexamethasone in group BD in addition to 10 mL epidural plain bupivacaine 0.25%. This study showed that both combinations had the same effect concerning the use of postoperative opioids' need and antiemetic effects.[17] The results of this study also go in accordance with a study done by Thomas and Beevi, which was a randomized, double-blind study, including 94 patients who underwent laparoscopic cholecystectomy procedure who were divided into three groups randomly. The study showed that preoperative epidural dexamethasone 5 mg given with or without bupivacaine decreases postoperative pain and opioids' need.[18] Also, the results of this study go in accordance with a study done by Elham M El-feky *et al.*, whose study compared hemodynamics during the operation, pain relief, and sedation and side effects of fentanyl, dexmedetomidine, and dexamethasone postoperatively used as adjuvants to bupivacaine in pediatrics having caudal analgesia, including 120 patients (3–10 years old) undergoing lower abdominal surgeries under general anesthesia. This study showed that dexmedetomidine and dexamethasone are good alternatives when added to bupivacaine in prolongation of pain relief after the operation compared with local anesthetic alone or added to fentanyl, all used in caudal anesthesia. Also, they showed less side effects compared with caudal fentanyl.[19] In a study done by Kirksey *et al.*, which was a systematic review of adjuvant-related randomized controlled trials and meta-analyses and providing recommendations for using adjuvants in peripheral nerve blocks, between 1990 and 2014, they concluded that some agents are considered promising in prolonging the effect of local anesthetic in nerve blocks such as buprenorphine, clonidine, dexamethasone, magnesium, and dexmedetomidine. However, using any perineural adjuvant must be done with caution, because none of them is approved by the Food and Drug Administration, and concerns for drawbacks and toxicity still exist.[20] Some studies were against the finding of the current one, such as done by Lotfinia *et al.*, which evaluated the use of epidural methylprednisolone or bupivacaine for postsurgical lumbar discectomy pain relief in a randomized, placebo-controlled trial. In conclusion, postoperative back and radicular pain are not relieved by administration of epidural methylprednisolone or bupivacaine intraoperatively.[21] Also, in a study carried out by Abdel-Aleem *et al.*, evaluating the strength of 8 mg dexamethasone when added to intrathecal bupivacaine had no effect on VAS and postoperative opioids' consumption in cesarean section candidates.[22] The results of this study are against the findings of Amira Fathy Hefni *et al.* In this study patients were divided into four groups to be given a total volume of 10 mL of epidural plain bupivacaine 0.25% in the control group (Group D0) with either 4 mg dexamethasone (Group D4) or 6 mg dexamethasone in (Group D6) or 8 mg dexamethasone (Group D8), and then were generally anesthetized. The conclusion was that higher doses of dexamethasone given to patients were more efficient at controlling moderate to severe pain than lower doses.[23] Also, the results of this study showed that no significant complications occurred after addition of dexamethasone to levobupivacaine. Neonatal harm as a result of epidural anesthesia is quite doubtful. No remarkable difference in neonatal outcome was discovered between the studied groups, indicated by several factors such as a normal Apgar score and the absence of naloxone need or neonatal mechanical ventilation. This was in line with the results of Liu *et al.*, who performed meta-analysis of seven randomized controlled trials to compare low-concentration epidural infusions to parenteral opioids.[24]

Limitations to our study were that the dose of epidural dexamethasone and the timing of its administration during the course of labor need further research to reach the optimum length of analgesic period during labor with the lowest cumulative dose of local anesthetic consumed. Postpartum analgesia is another advantage that may be gained with the use of dexamethasone, but this is beyond the scope of this study. Finally, a larger number of patients could be studied in future researches to increase the strength of the study.

Conclusion

Epidural dexamethasone plus levobupivacaine prolongs the duration of spinal analgesia during combined spinal-epidural for management of labor pain, with hemodynamic stability and limited maternal and neonatal adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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