

# The effect of addition of dexamethasone to levobupivacaine in parturients receiving combined spinal-epidural for analgesia for vaginal delivery

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## ABSTRACT

**Background and Aims:** Regional analgesia is commonly used for the relief of labour pain, Prolongation of analgesia can be achieved by adjuvant medications. The aim of this randomised controlled trial was to evaluate the efficacy of intrathecal levobupivacaine with dexamethasone for labour analgesia. **Methods:** A total of 80 females were included in this study, all were primigravidas undergoing vaginal delivery with cervical dilatation  $\geq 4$  cm and 50% or more effacement. Forty females were included randomly in either Group L (received intrathecal levobupivacaine 0.25% in 2 mL) or Group LD (received intrathecal levobupivacaine 0.25% combined with dexamethasone 4 mg in 2 mL). The primary outcome was the duration of spinal analgesia. Secondary outcomes included the total dose of epidural local anaesthetic given, time to delivery, neonatal outcome and adverse effects. **Results:** The duration of spinal analgesia was significantly longer in the LD group compared with L group ( $80.5 \pm 12.4$  min vs.  $57.1 \pm 11.5$  min, respectively;  $P < 0.001$ ). In Group LD compared with Group L, time from spinal analgesia to delivery was significantly lower ( $317.4 \pm 98.9$  min vs.  $372.4 \pm 118.8$  min, respectively;  $P = 0.027$ ), and total epidural levobupivacaine consumption was significantly lower ( $102.4 \pm 34.8$  mg vs.  $120.1 \pm 41.9$  mg, respectively;  $P = 0.027$ ). The two groups were comparable with respect to characteristics of sensory and motor block, haemodynamic parameters, pain scores, neonatal outcome and frequency of adverse effects. **Conclusion:** Intrathecal dexamethasone plus levobupivacaine prolongs the duration of spinal analgesia during combined spinal-epidural CSE for labour analgesia.

**Key words:** Combined spinal-epidural, dexamethasone, intrathecal, levobupivacaine

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## INTRODUCTION

The era of obstetric anaesthesia started with James Young Simpson, who administered ether to a woman during childbirth.<sup>[1]</sup> Various techniques including inhalational nitrous oxide, parenteral opioids, acupuncture and hydrotherapy were used to decrease the pain and trauma of labour. Opioids provide only mild to moderate analgesia in the safe doses which do not result in maternal sedation and respiratory depression or neonatal depression.<sup>[2]</sup> Nowadays, neuraxial analgesia is considered the most effective method of labour analgesia, and results in minimal maternal and foetal respiratory depression. Epidural analgesia was used to relieve labour pain for the past 50 years. However, a recent study concluded that

combined spinal-epidural (CSE) analgesia with an intrathecal levobupivacaine - fentanyl combination is superior to epidural analgesia alone as well as to patient-controlled intravenous (IV) analgesia with remifentanyl for analgesia in early labour.<sup>[3]</sup> Levobupivacaine, the S-enantiomer of bupivacaine is a newer local anaesthetic agent that possesses lower cardiac and neural toxicity.<sup>[4]</sup>

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Dexamethasone relieves pain through reducing inflammation and blocking of nociceptive C-fibres transmission and by suppressing neural ectopic discharge.<sup>[5]</sup> Post-operative analgesic effectiveness and duration was prolonged when dexamethasone was used as an adjunct for peripheral nerve blocks.<sup>[6]</sup> Recent studies reported no complications associated with intrathecal dexamethasone.<sup>[7]</sup>

The aim of this study is to compare the efficacy of intrathecal levobupivacaine alone versus a combination of levobupivacaine with dexamethasone on the duration of spinal analgesia in normal vaginal deliveries, and to determine whether addition of dexamethasone to levobupivacaine for spinal analgesia will reduce the amount of epidurally administered analgesic drugs and shorten the time from spinal analgesia to delivery.

## METHODS

This prospective double-blinded trial, which was approved by the institutional review board, included eighty primigravida women between 18 and 35 years of age, American Society of Anesthesiologists' (ASA) physical status 1 or 2 scheduled for vaginal delivery. All participants provided informed consent to be involved in the study. They were included when the cervix was dilated 4 cm or more with 50% or greater effacement. Excluded subjects were the ones who refused to participate, those with ASA physical status III or higher, those with diagnosed foetal abnormalities, or having contraindications to regional anaesthesia and the use of the study drugs due to known allergy. Patients were then randomly assigned into one of two groups using closed envelope technique according to the type of intrathecal analgesia given; Group L ( $n = 40$ ) received intrathecal levobupivacaine hydrochloride 0.25% (Chirocaine®, Abott Lab., Italy) in normal saline in a total volume of 2 mL and Group LD ( $n = 40$ ) received intrathecal levobupivacaine 0.25% in normal saline combined with 4mg preservative free dexamethasone (Dexadic®, Caspian Tamin Pharmaceutical Co., Iran) in a total volume of 2 mL.

At inclusion, a venous line was established, and lactated Ringer's solution 15 ml/kg was given. All women were monitored with non-invasive blood pressure, pulse oximetry and electrocardiography in addition to cardiotocography. Analgesia was then initiated with the CSE technique by an anaesthesiologist blinded to the drug injected. Another anaesthesiologist not

involved in the study prepared the drug syringes. With the patient in the sitting position the epidural space was identified with a 17-gauge Tuohy needle (Perifix®, Braun, Germany), at the L<sub>2</sub>-L<sub>3</sub> or L<sub>3</sub>-L<sub>4</sub> interspace using loss-of-resistance to air technique. Through the Tuohy needle, a 19-gauge epidural catheter (Perifix®, Braun, Germany) was inserted and secured 3-4 cm into the epidural space. Absence of blood or CSF on aspiration was confirmed. Under sterile conditions, the skin was infiltrated with 2% lidocaine in the midline, and lumbar puncture was performed at the lower interspace (L<sub>3</sub>-L<sub>4</sub> or L<sub>4</sub>-L<sub>5</sub>), using a 25-gauge Whitacre spinal needle. Drugs were injected intrathecally for spinal analgesia as per the group allocation. Thirty seconds after intrathecal injection, women were allowed to lie down in the supine position with left lateral uterine displacement to prevent aortocaval compression, oxygen was provided by facemask at 2-4 L/min. The onset of spinal analgesia was identified by the loss of pinprick sensation at T<sub>10</sub>.

At the first request of analgesia, a combination of 0.25% levobupivacaine with 100 µg fentanyl in a volume of 10 ml was injected through the epidural catheter. Further analgesia was provided with 7 ml 0.25% levobupivacaine hourly.

All women were followed up until delivery on a partogram with assessment of pain, sensory and motor block, mean arterial blood pressure (MAP), heart rate (HR), oxygen saturation and appearance of adverse effects. The primary outcome of the study was the duration of spinal analgesia which was defined as the time between the onset of analgesia and the first request of additional analgesia. Secondary outcome measures were time from spinal analgesia to delivery, total amount of epidurally administered levobupivacaine, pain scores, characteristics of sensory and motor block, haemodynamic stability, adverse effects of neuraxial block (nausea, vomiting, shivering, pruritis, sedation and urinary retention) and neonatal outcome.

Pain was assessed on visual analogue scale (VAS) (0 = no pain and 10 = worst pain possible) at baseline, and at 20 min after the spinal analgesia. Level of sensory block was determined by loss of pinprick sensation using a 20-gauge hypodermic needle. A modified Bromage scale (0 = no motor block, 1 = hip blocked, 2 = hip and knee blocked, 3 = hip, knee and ankle blocked) was used to assess motor blockade at 1, 5 and 20 min after intrathecal injection.

Maternal hypotension was defined as a systolic arterial pressure <90 mmHg or >30% decrease from the baseline. It was treated by increasing the IV infusion rate or IV ephedrine 10 mg boluses, if necessary. Maternal bradycardia (heart rate less than 50 beat/min) was treated with atropine 0.6 mg increments. Oxygen saturation below 94% was treated with increased supplemental oxygen. Foetal bradycardia <110 beats/min, late or variable decelerations were documented and an obstetrician was consulted if necessary.

Neonatal outcome was assessed in terms of umbilical vein blood pH and Apgar score at 1 and 5 min after delivery. After delivery, maternal satisfaction was evaluated on a 0–3 score (0 = poor, 1 = fair, 2 = good, and 3 = excellent).

Sample size calculations were performed for the unpaired *t*-test for independent samples with time to analgesic supplementation in the two groups as the primary outcome variable in the present study. Previous studies showed that the standard deviation of time for analgesic supplementation in levobupivacaine + dexamethasone group was about 7.8 h, with a mean of 13 h,<sup>[8]</sup> and standard deviation of time for analgesic supplementation was 4.8 h, with a mean of 6.1 h in the levobupivacaine group.<sup>[8]</sup> Taking power 0.9 and alpha error 0.05, a minimum sample size of thirty patients was calculated for each group. A total number of forty 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. The value of  $P < 0.05$  was considered statistically significant.

## RESULTS

Eighty patients completed the study protocol. There was no statistically significant difference concerning age, body mass index, gestational age, cervical dilatation before analgesia, the cervical effacement and frequency of instrumental delivery between the two groups [Table 1].

The duration of spinal analgesia was significantly higher ( $P < 0.001$ ) while the time from the spinal analgesia to delivery was significantly lower ( $P = 0.027$ ) in Group LD than Group L. Furthermore, a noticeable decrease

in the levobupivacaine consumption was found in Group LD compared to the Group L ( $P = 0.049$ ). The VAS was comparable before the block in both groups ( $P = 0.416$ ). Significant reduction in VAS score was observed in both groups 20 min after block. However, the post-block VAS score was not noticeably different ( $P = 0.644$ ) [Table 2].

Both groups showed comparable characteristics of motor and sensory blockade [Table 3]. Haemodynamically, the two groups were comparable regarding the changes in MAP and HR [Figures 1 and 2]. There was no significant difference between the groups concerning neonatal outcome and the frequency of nausea, vomiting and shivering [Table 4].

## DISCUSSION

In this study, we found that the addition of 4mg dexamethasone intrathecally to 2.5 mg of

**Table 1: Demographic and clinical characteristics of the two studied groups**

Demographic and clinical characteristics	Group L	Group LD	P
Age (year)	26.2±4.7	26.8±5.1	0.587
BMI (kg/m <sup>2</sup> )	24.2±2.1	24.1±2.0	0.869
Gestational age (week)	39.0±0.9	38.8±0.8	0.366
Cervical dilation before analgesia (cm)	4.5±0.8	4.7±0.6	0.284
Cervical effacement (%)	55.3±9.3	52.5±10.3	0.215

Data are presented as mean±SD, or *n* (%). SD – Standard deviation; BMI – Body mass index

**Table 2: Analgesic profile in the two studied groups**

Analgesic profile	Group L	Group LD	P
Duration of analgesia (min)	57.1±11.5	80.5±12.4	<0.001
Time from spinal analgesia to delivery (min)	372.4±118.8	317.4±98.9	0.027
Total amount of levopubivacaine (mg)	120.1±41.9	102.9±34.8	0.049
VAS score (Median [IQR])			
Before the block	7 (6-9)	7 (5-9)	0.416
After the block by 20 min	2 (0-2)	2 (0-2)	0.644

Data are presented as mean±SD and median (IQR). VAS – Visual analogue scale; SD – Standard deviation. IQR- (Interquartile range)

**Table 3: Characteristics of sensory and motor block in the two studied groups**

Characteristics of sensory and motor block	Group L	Group LD	P
Time to onset of sensory block at T10 (min)	8.6±1.8	9.0±1.5	0.313
Time to highest sensory level (min)	13.6±1.5	13.4±1.6	0.567
Frequency of motor block, <i>n</i> (%)	3 (7.5)	4 (10.0)	0.348
Bromage scale [Median (IQR)]	0 (0-2)	0 (0-3)	0.314
Frequency of instrumental delivery, <i>n</i> (%)	7 (17.5)	6 (15)	0.762

Data are presented as mean±SD, *n* (%), or median (IQR). SD – Standard deviation IQR (Interquartile range)

levobupivacaine in CSE for labour analgesia prolonged the duration of spinal analgesia. In addition, it shortened the time from spinal analgesia to delivery and reduced epidural levobupivacaine consumption. Intrathecal dexamethasone did not alter level of and time to highest sensory block, and there were no adverse motor effects. It did not also modify pain intensity or haemodynamic parameters. Neonatal outcome and frequency of adverse effects did not change with dexamethasone use.

We preferred levobupivacaine for intrathecal labour analgesia as it has less cardiovascular and neurologic adverse effects and less motor block compared to bupivacaine.<sup>[9]</sup> We studied dexamethasone as an adjuvant because of its efficacy, safety and low cost. Its exact mechanism of analgesia is not yet clearly understood.<sup>[10-12]</sup> Some authors claim that the mechanism is related to its anti-inflammatory effect that inhibits algogenic substances such as

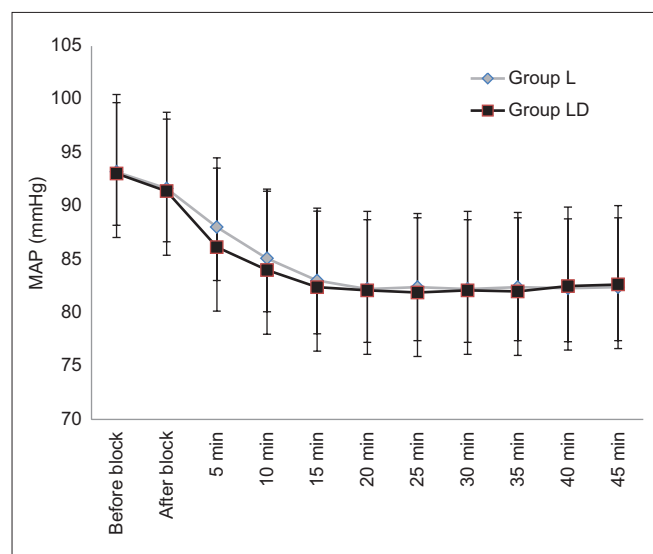
prostaglandins, glutamate and substance P in the spinal cord.<sup>[13]</sup> Others claim that its membrane stabilization effect is achieved by modifications in the potassium channels.<sup>[14]</sup>

The results of this study are similar to a study of intrathecal dexamethasone as an adjuvant to bupivacaine in 50 patients undergoing orthopaedic surgery. In that study, the dose of dexamethasone used was 8mg. The results showed a favourable effect of bupivacaine plus dexamthasone on postoperative analgesia and duration.<sup>[7]</sup> In another study, lignocaine plus dexamethasone 4 mg was compared to lignocaine plus 100 µg epinephrine intrathecally in patients undergoing cesarean section. This study found that dexamethasone increased the sensory block duration and prolonged the duration of analgesia more than epinephrine.<sup>[15]</sup> These results were not reproduced in a study in which the prolongation of motor and sensory block with the addition of dexamethasone (8 mg) to lignocaine for spinal anesthesia was similar to that [provided by the addition of epinephrine (0.2 mg) to lidocaine 5%.<sup>[16]</sup> An excellent and long-lasting analgesic effect was achieved when methylprednisolone was added to bupivacaine intrathecally in patients with post-herpetic neuralgia.<sup>[17]</sup> Similarly, a study that tested dexamethasone through the epidural route found that dexamethasone (5 mg) in patients having cholecystectomy decreased post-operative pain either alone or in combination with bupivacaine.<sup>[18]</sup> Moreover, dexamethasone as an adjuvant to local anaesthetics during brachial plexus block was shown to improve the quality of analgesia without adverse-effects.<sup>[19-22]</sup> Although there were many reviews and meta-analysis focused on the studies that were done regarding adjuvants injected in local anaesthetic nerve blocks, there is no meta-analysis or review that focuses on the adjuvants used through the intrathecal route.<sup>[23]</sup> Some

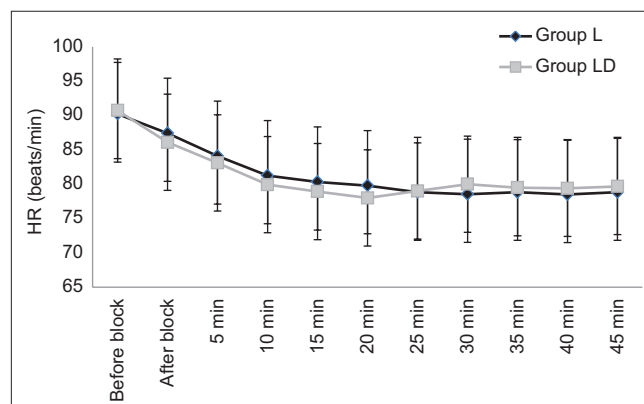
**Table 4: Neonatal outcome and frequency of intrapartum complications in the two studied groups**

Neonatal outcome and frequency of intrapartum complications	Group L	Group LD	P
pH of umbilical vein blood	7.41±0.05	7.39±0.08	0.232
Apgar score (Median [IQR])			
After 1 min	8 (6-9)	8 (6-9)	0.377
After 5 min	10 (8-10)	10 (7-10)	0.514
Intrapartum complications, n (%)			
Nausea	6 (15.0)	2 (5.0)	0.23
Vomiting	4 (10.0)	2 (5.0)	0.20
Shivering	5 (12.5)	6 (15.0)	0.37

Data are presented as mean±SD, n (%), or median (IQR). SD – Standard deviation IQR (Interquartile range)



**Figure 1:** Changes of the mean arterial pressure over time in the two studied groups



**Figure 2:** Heart rate changes over time in the two studied groups

authors failed to find a prolonged analgesic effect of steroids postoperatively. One of them used epidural methylprednisolone as an additive to bupivacaine for pain relief after lumbar discectomy and found no difference in analgesic duration compared to bupivacaine alone.<sup>[24]</sup> Another study used the intrathecal route but found that it is not effective in the analgesic duration.<sup>[25]</sup>

Our findings are similar to studies which did not report any complications from the use of intrathecal dexamethasone.<sup>[7,17]</sup>

Lastly, concerning the neonatal outcome there were no harm recorded in this study. Also regarding the frequency of nausea, vomiting and shivering, records showed significant reduction in their incidence.

Considering the limitations of our study, we think that the dose of intrathecal dexamethasone and the timing to initiate spinal analgesia need further research to reach the optimum length of analgesic period during labour with the lowest cumulative dose of local anaesthetic consumed in CSE technique. Post-partum analgesia is another advantage that may be gained with the use of intrathecal dexamethasone, however this is beyond the scope of the current study

## CONCLUSION

Intrathecal dexamethasone plus levobupivacaine prolongs the duration of spinal analgesia during combined spinal-epidural for the management of labour pain, with haemodynamic 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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