Comparison of Intrathecal Levobupivacaine and Levobupivacaine-Morphine for Caesarean Delivery (Randomized Study)

Sezaryen Uygulamalarında İntratekal Levobupivakain ve Levobupivakain-Morfinin Karşılaştırılması

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ABSTRACT Objective: To compare intrathecal levobupivacaine and levobupivacaine-morphine for caesarean delivery according analgesic requirement, haemodynamic effects, "activity, pulse, grimace, appearance and respiration (APGAR)" scores, side effects and patients' satisfaction. **Material and Methods:** This study took place in Suleyman Demirel University,Department of Anesthesiology and Reanimation, Isparta, Turkey between October 2006-June 2007. The patients were randomly assigned into two groups of 15 patients group L received levobupivacaine 10 mg, group LM levobupivacaine 10 mg + 0.01 mg morphine. Lumbar puncture was performed at the L3-L4 interspace Sensory block level was evaluated with bilateral pinprick test and motor block by Bromage scale. Anesthesia induction to delivery time, skin incision to delivery time, time and duration of surgery were recorded. Apgar scores were recorded at 1st, and 5th min. Postoperative occurrence of maternal side-effects such as nausea, vomiting, pruritus, or respiratory depression were recorded. The time to the first postoperative request for an analgesic was also recorded. Statistical analysis was performed by using non-parametric Mann Whitney U, Chi square tests and p value < 0.05 was considered to be significant. **Results:** Demographical data were similar in both groups. Time to maximum bromage (Bromage score 3) and maximum sensory block level were similar. There was a significant difference between the two groups for the time to first analgesic request. Six patients in group LM didn't require any analgesic. **Conclusion:** Morphine-levobupivacaine combination provided longer duration of postoperative analgesia in caesarean section eventhough there were not significant differences between the groups according side effects, patients' satisfaction and APGAR scores when compared with levobupivacaine.

Key Words: Levobupivacaine; caesarean section; APGAR score; anesthesia, spinal

ÖZET Amaç: Bu çalışmada, sezaryen uygulamalarında intratekal levobupivakain ve levobupivakain-morfinin analjezik ihtiyacı, hemodinamik etkiler, "activity, pulse, grimace, appearance and respiration (APGAR)" skorları ve hasta memnuniyetine göre karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışma Süleyman Demirel Üniversitesi, Anesteziyoloji ve Reanimasyon Anabilim Dalında, Isparta, Türkiye'de Ekim 2006-Haziran 2007 tarihleri arasında yapıldı. Hastalar randomize olarak 15'er kişilik iki gruba ayrıldı. Grup L'ye 10 mg levobupivakain, grup LM'ye ise 10 mg levobupivakain + 0.01 mg morfin L3-L4 seviyeden spinal aralığa girilerek uygulandı. Duyu bloğu yüksekliği bilateral pinprick testi ve motor blok "Bromage" skala ile değerlendirildi. Anestezi indüksiyonu-doğum zamanı, cilt insizyonu-doğum zamanı ve cerrahi süre kaydedildi. APGAR skorları 1.ve 5. dakikalarda, postoperatif bulantı, kusma, kaşıntı ve solunum depresyonu gibi maternal yan etkiler de kaydedildi. Ayrıca postoperatif ilk analjezik gereksinim zamanı da kaydedildi. İstatistiksel analizler non-parametrik Mann Whitney U, ki-kare testleri kullanılarak yapıldı ve p< 0.05 anlamlı kabul edildi. **Bulgular:** Demografik veriler her iki grupta benzerdi. Maksimum Bromage ve maksimum duyu bloğu zamanları benzer bulundu. İlk analjezik ihtiyaç zamanında gruplar arasında anlamlı fark gözlendi. Grup LM'de altı hastanın analjezik ihtiyacı olmadı. **Sonuç:** Morfin-levobupivakain kombinasyonunda yan etki, hasta memnuniyeti ve APGAR skorları arasında istatistiksel olarak fark bulunmamasına rağmen, levobupivakain alan gruba göre daha uzun postoperatif analjezi süresi gözlendi.

Anahtar Kelimeler: Levobupivakain; sezaryen; APGAR skor; spinal anestezi

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Levobupivacaine, the pure S(-)-enantiomer of racemic bupivacaine, has recently been introduced for routine obstetric[1] and non-obstetric[2] spinal and epidural anaesthesia, peripheral nerve blocks[3] and infiltration analgesia.[4]

Levobupivacaine has showed a lower risk of cardiovascular and central nervous system (CNS) toxicity than bupivacaine not only in animal studies, but also in human volunteers: it has less negative inotropic effect, less effect on the duration of the QRS complex and intravenous doses >75 mg, produces less prolongation of the QTc interval and less decrease of the stroke index than bupivacaine.[5]

A single dose of intrathecal (IT) morphine decreases postcaesarean opioid analgesic requirements and may reduce or prevent neonatal neurobehavioral depression associated with maternal analgesia.[6]

The perioperative circumstances for caesarean section are different from those of other operations. The mother is usually free of disease and ideally she should be able to walk to the neonatal unit as soon as possible to have contact with her child and to breast feed. Early mobilization decreases the postoperative risk of venous thrombosis decreases. The quality of anesthesia and maternal satisfaction with child birth are influenced by a number of factors including perioperative pain, side effects of anesthesia (e.g. nausea and vomiting, pruritus, somnolance and numbness of legs), anxiety, impression of childbirth, condition of the newborn and caregiver support.[7]

The aim of this prospective, double-blind randomized study was to compare the analgesia, spinal block characteristics, "activity, pulse, grimace, appearance, and respiration (APGAR)" scores and patients' satisfaction of levobupivacaine and levobupivacaine plus morphine given intrathecally for caesarean section.

MATERIAL AND METHODS

After obtaining institutional ethical committee approval and written informed consent, 30 healthy (ASA I or II) parturients scheduled for caesarean section of single babies at term were included in the study. The indication for caesarean section were either primary elective or repeat caesarean section with no evidence of fetal distress in any of the patients.The inclusion criteria were parturients at term (gestation week 36-41), age ≥ 18 years, height ≥ 150 cm, body weight ≤ 110 kg, singleton fetus and estimated fetal weight ≥ 2500 g. Exclusion criteria were preeclampsia and a history of allergies, sensitivity or any other form of reaction to local anesthetics of amide type. All patients were instructed on the use of visual analogue scale (VAS) (0= No pain, 10= Worst possible pain) on the day before operation and the doctor blind to the medication evaluated the patients. The parturients had nothing per os for six hours and were not given any premedication.

The patients were randomly assigned according to a computer-generated random number list into two groups of 15 patients group L received levobupivacaine. 0.5% 10 mg (2 mL) plus 0.5 mL saline, group LM received levobupivacaine 0.5% 10 mg (2 mL) plus 0.01 mg morphine (0.5 mL) intrathecally. Routine monitoring devices (ECG, pulse oximetry, non-invasive blood pressure monitor, Datex-Ohmeda, Instrumentorium Corp., Helsinki, Finland) were attached.

After intravenous pre- hydration with NaCl 0.9% (750 mL) parturients were placed in the sitting position. Lumbar puncture was performed at the L3-L4 interspace with a 27-G spinal needle (Quincke, Exelint, Los Angeles, USA). After free flow of cerebrospinal fluid was observed the injection was completed within 10 seconds and the parturients were placed in the supine with a left lateral tilt and a pillow under the thigh. Nasal oxygen (2 L min^{-1}) was given until delivery.

Sensory block level was evaluated with bilateral pinprick test at midclavicular level, every 2 min until it reached T5 level and then every 10 min during procedure by the doctor who did not know the given medication. The following variables were recorded: time to initial onset of analgesia, time for sensory block to reach the T5 dermatome, time to maximum cephalad spread of analgesia, time to two segment regression of analgesic level.

Motor block was evaluated every 2 min using Bromage scale (0= None, 1= Ability to flex knees, but not the hips, 2= Unable to flex knees, but no problems with ankle movement, 3= No movement pos-

sible in any lower extremity) until complete motor block and then 15 min until the return of normal motor function. Complete motor block and motor block score at the sensory level of T5 were recorded.

Time between skin incision and delivery was also recorded (Table 1). Umblical blood samples were collected for blood gasses analysis and APGAR scores at 1st and 5th min were evaluated and recorded.

Postoperative analgesia was evaluated at every 15 minutes by using VAS and diclofenac 75 mg was given as a rescue analgesic to the patients whose VAS > 3 and the time was recorded as the time of first analgesic need. During the operation sedation and general anesthesia requirements and occurrence of maternal side-effects such as nausea, vomiting, pruritus, or respiratory depression were recorded. Metoclopramide 10 mg were given for vomiting or after two successive episodes of nausea and Diphenhydramine 20 mg for pruritus. Hypotension was treated by fluid loading and 5 mg ephedrine intravenously. Bradycardia was defined as a heart rate (HR) below 55 beats.min^{-1} and was treated with 0.01-0.02 mg.kg^{-1} atropine. Side effects such as pruritus, headache, backache, respiratory depression, nausea-vomiting were recorded for postoperative 48 hours.

Surgeon was asked for the quality of anesthesia and muscle relaxation and the parturient for intraoperative comfort and the data were recorded as exellent, good, fair or poor.

STATISTICAL ANALYSIS

The duration of postoperative analgesia and APGAR scores were used for power analysis. Statistical analysis was performed by using SPSS (SPSS for Windows Release 10.0) statistical package. Continuous variables such as mean arterial pressure and heart rate were analyzed with Student's t-tests. Nominal or ordinal variables were analyzed by Chi-square and Mann Whitney U tests. $p < 0.05$ was considered to be significant.

RESULTS

The patient characteristics, obstetric and surgical variables were similiar in two groups (Table 1, 2). There were not any statistically significances between the groups according intraoperative crystalloid use and ephedrine doses (Table 3).

Spinal block was succesfully performed and all patients completed the study. None of the patients required additional analgesia, sedation or general anesthesia. There were no differences between the groups in time to reach the T5 sensory level, maximum level of sensory block, motor block scores (Bromage scale) when the sensory level reached T5. The time to reach complete motor block (Bromage score 3) was shorter and the time to complete recovery from motor block was longer in the levobupivacaine + morphine group than levobupivacaine group but it was not significant statistically ($p > 0.05$) (Table 3).

The time to regression of two dermatomes was similiar in the two groups ($p > 0.05$). The mean time to first complaint of pain were 254 ± 186 min in group L and 606 ± 416 min in group LM and there was a significant differences between the groups ($p < 0.05$). Six patients in LM group did not require any analgesic (Table 3).

Mean arterial pressure decreased 5 min after spinal block but it was not significant (Table 4). Total ephedrine requirements were higher in group LM but the number of patients who required ephedrine was almost similiar; 9 in group L and 10 in group LM (Table 3).

TABLE 1: Surgical variables. Data are mean ± SD.

	Levobupivacaine	Levobupivacaine-morphine
Induction-delivery time (min)	19.8 ± 4.83	21.8 ± 6.12
Skin incision-delivery time (min)	5 ± 1.2	7 ± 3.4
Duration of surgery (min)	50 ± 12.8	50.2 ± 13.6

TABLE 2: Patients variables. Data are mean ± SD.

	Levobupivacaine	Levobupivacaine-morphine
Age (year)	27.3 ± 4.2	28.6 ± 6.5
Height (cm)	159 ± 5.5	160 ± 4.6
Weight (kg)	75.2 ± 10.5	77.6 ± 10.2
Gestational age (week)	39 ± 2.7	39 ± 2.9
ASA I/II	14/1	15/0

TABLE 3: Characteristics of spinal anesthesia and postoperative analgesic request time. Data are mean ± SD.

	Levobupivacaine	Levobupivacaine -morphine
Sensory block		
Time to T5 (min)	6.2 ± 4.85	4.86 ± 2.82
Maximum block level	T5 ± 2.1	T4 ± 1.7
Time of regression (min)	75.6 ± 19.1	75.6 ± 18.3
Motor block		
Bromage score at T5 sensory block	2 ± 0.53	2.26 ± 0.59
Time to maximum block (min)	7 ± 8.2	4.6 ± 4
Complete block at T5 (patient) (bromage score 3)	2 ± 0.7	5 ± 0.4
Sympathetic block		
Ephedrine required	9	10
Time first analgesic request (min)	254 ± 186	*606 ± 416

*p< 0.05 between the groups.

TABLE 4: Haemodynamic profile. Data are mean ± SD.

	Levobupivacaine	Levobpivacaine-morphine
Baseline		
HR (beats min -1)	98.4 ± 15	100 ± 17
MAP (mmHg)	110.2 ± 12	103 ± 9.1
5 min after block		
HR (beats min -1)	110 ± 19.5	110.8 ± 17.4
MAP (mmHg)	*89.4 ± 28.6	*98.4 ± 20.8
After incision		
HR (beats min -1)	98.4 ± 26.5	91.6 ± 22.5
MAP (mmHg)	82 ± 14.4	81.1 ± 13.2
10 min after incision		
HR (beats min -1)	98.6 ± 22.7	95.1 ± 15.1
MAP (mmHg)	89.4 ± 10.8	81.2 ± 10.7
20 min after incision		
HR (beats min -1)	97.1 ± 19.4	94.9 ± 15.4
MAP (mmHg)	87.7 ± 14.7	82.1 ± 15.3
Baby delivery		
HR (beats min -1)	96.2 ± 20.7	93.3 ± 17.3
MAP (mmHg)	74.8 ± 17.1	72.8 ± 23

HR: Heart rate; MAP: Mean arteria pressure.
*p> 0.05 according to the baseline value.

APGAR scores and umbilical venous pH values were within the normal range in both groups. The 1st min APGAR scores were 7.8 ± 1.2 and 7.8 ± 0.6 in the group L and LM, respectively, and 5th min APGAR scores were 9.9 ± 0.1 and 9.9 ± 0.2 (p> 0.05). The umbilical blood pH values of the group L and LM were 7.3 ± 0.03 and 7.32 ± 0.04, respectively (p> 0.05) (Table 5).

Almost similar numbers of patients in each group experienced nausea, vomiting and hypotension. Two patients had pruritus and one patient had headache in group LM (Table 6).

Quality of anaesthesia and muscle relaxation were similar in both groups. Surgeon's scores for 14 patients were excellent and for one patient good in group L and in group LM the scores were excellent for 15 patients

Patient satisfaction scores were excellent for all patients in group LM; in group L scores were excellent for 13 patients and good for two patients (p> 0.05).

DISCUSSION

Subaracnoid anesthesia is still popular for caesarean section because the technique is easy and brief for the parturient who finds it difficult to hunch up her back, and spinal local anaesthetics produce adequate relaxation of abdominal muscles with few effects on the neonates.[7] However, spinal anesthesia provides insufficient postoperative analgesia and additional analgesics are usually required in the postoperative period.[6] Levobupivacaine has been found to be as effective as racemic bupivacaine in spinal anesthesia.[8,9] Parpaglioni et al[10] has been studied the minimum lo-

TABLE 5: Neonatal condition. Data are mean ± SD.

	Levobupivacaine	Levobupivacaine-morphine
Neonatal weight (g)	3310 ± 455.36	3467 ± 329.42
APGAR 1 min	7.8 ± 1.2	7.8 ± 0.6
APGAR 5 min	9.9 ± 0.1	9.9 ± 0.2
Umbilical blood pH	7.3 ± 0.03	7.32 ± 0.04

APGAR: Activity, pulse, grimace, appearance, and respiration.

TABLE 6: Side effects. Data are number of patients (%).

	Levobupivacaine	Levobupivacaine-morphine
Nausea	7 (40)	8 (53)
Vomiting	2 (13)	2 (13)
Pruritus	-	2 (13)
Respiratory depression	-	-
Headache	-	1 (6)
Backache	-	-
Sedation	-	-
Shivering	-	-
Bradicardia	-	-
Hypotension	9 (60)	10 (66)

cal analgesic concentration (MLAC) model to determine the median effective dose (ED_{50}) of intrathecal levobupivacaine and ropivacaine for caesarean section and defines this as the minimum local anaesthetic dose,[8] and they found minimum local anaesthetic dose (MLAD) of levobupivacaine for caesarean section to be 11.1 mg using the formula of Dixon and Massey.[11] In our study we used 10 mg 0.5% levobupivacaine intrathecally as MLAD.

Morphine is the most important analgesic drug used in the management of postoperative pain[12] and intrathecal morphine for elective cesarean section greatly reduces postoperative patient analgesic need.[7]

A single dose of intrathecal morphine decreases postcaesarean opioid analgesic requirements and may reduce or prevent neonatal neurobehavioral depression associated with maternal analgesia.[6]

The addition of an opioid to the local anesthetic has been widely studied in the management of spinal anesthesia for caesarean delivery, but there is no consensus yet about the optimal choice of opioid and dosage Karaman et al[13] used intrathecal sufentanil 5 μg in their study and showed that opioid had not any gross effects on the neonate.[13]

Katsuyuki et al[7] used intrathecal 0.02 mg morphine with hyperbaric bupivacaine 0.5% and showed that the duration of complete analgesia and the time to request for additional analgesics were longer in bupivacaine group than in bupivacaine morphine group. Combination of intrathecal morphine is less expensive than the new pain management technologies currently in use.[7] We preferred 0.01 mg morphine for the study to see if that much additional opioid had the same effect as the other doses studied before.

Ogun et al[14] showed that intrathecal isobaric ropivacaine 0.5% 15 mg plus morphine provided sufficient anaesthesia for caesarean delivery and the ropivacaine-morphine combination resulted in shorter motor block, similar sensory block and postoperative analgesia with respect to the same combination of bupivacaine-morphine.[11,14] Intrathecal morphine for caesarean delivery increased the duration of postoperative analgesia without increasing maternal or neonatal side effects.[13]

In patients undergoing caesarean section with spinal anaesthesia, intrathecal opioids may cause additional nausea, vomiting, pruritus, urinary retention and respiratory depression due to μ and κ opioid receptor activations.[15] We thought that because of using small doses of morphine in this study we did not find any severe side effects.

In our study 0.01 mg additional morphine to levobupivacaine provided longer duration of postoperative analgesia without any effect on APGAR scores and serious side effects. We found out that both groups provided satisfactory spinal block according surgeons' and patients' excellent satisfaction.

REFERENCES

1. Bader AM, Tsen LC, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. Anesthesiology 1999;90(6): 1596-601.
2. Bay-Nielsen M, Klarskov B, Bech K, Andersen J, Kehlet H. Levobupivacaine vs bupivacaine as infiltration anaesthesia in inguinal herniorrhaphy. Br J Anaesth 1999;82(2):280-2.
3. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg 2000;90(3):642-8.
4. Cox CR, Checketts MR, MacKenzie N, Scott NB, Bannister J. Comparison of S(–)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 1998;80(5):594-8.
5. McClellan KJ, Spencer CM. Levobupivacaine. Drugs 1998;56(12):355-62.
6. Wittels B, Glosten B, Faure EA, Moavad AH, İsmail M, Hibbard J, et al. Postcesaean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomess among nursin neonates. Anesth Analg 1997;85(3):600-6.
7. Katsuyuki T. Efficacy of intrathecal morphine for analgesia following effective cesarian section: comparison with previous delivery. J Med Sch 2003;70(4):327-33.
8. Glaser C, Marhofer P, Zmipfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg 2002;94(1):194-8.
9. Lee YY, Muchhal K, Chan CK, Cheung AS. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. Eur J Anaesthiol 2005;22(12):899-903.
10. Parpaglioni R, Frigo MG, Lemma A, Sebastiani M, Barbati G, Celleno D. Minimum local anaesthetic dose (MLAD) of intrathecal levobupivacaine and ropivacaine for Caesarean section Anaesthesia 2006;61(2):110-5.
11. Celleno D, Parpaglioni R, Frigo MG, Barbati G. Intrathecal levobupivacaine and ropivacaine for cesarean section. New perspectives. Minerva Anestesiol 2005;71(9):521-5.
12. Uchiyama A, Nakano S, Ueyama H, Nishimura M, Tashiro C. Low dose intrathecal morphine and pain relief following caesarean section. Int J Obstet Anesth 1994;3(2):87-91.
13. Karaman S, Kocabas S, Uyar M, Hayzaran S, Firat V. The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. European Journal of Anaesthesiology 2006;23(4):285-91.
14. Ogun CO, Kirgiz EN, Duman A, Okesli S, Akyurek C. Comparison of intrathecal isobaric bupivacaine-morphine and ropivacaine-morphine for caesarean delivery. Br J Anaesth 2003;90(5):659-64.
15. Stoelting RK. Opioid agonists and antagonists. In: Stoelting RK, eds. Pharmacology and Physiology in Anesthetic Practice. 3rd ed. Philadelphia: Lippincott-Raven Publishers; 1999. p.77-112.