Trakya Univ Tip Fak Derg 2009;26(3):214-219

Original Article / *Klinik Çalışma - Araştırma*

Comparison of Three Different Doses of Intrathecal Levobupivacaine in Urological Surgery

Ürolojik Cerrahide Üç Farklı İntratekal Levobupivakain Dozunun Karşılaştırılması

Hüseyin ŞEN, Mert AKBAŞ, Ali SIZLAN,[1] Ferhat ATEŞ,[2] Kamer DERE, İlker GÜNDÜ, Sezai ÖZKAN, Güner DAĞLI

Departments of Anesthesiology and Reanimation, [2]Urology, Gülhane Military Medical School Haydarpaşa Training Hospital, İstanbul; [1]Department of Anesthesiology and Reanimation, Gülhane Military Medical School, Ankara

Submitted / Başvuru tarihi: *07.09.2008* ***Accepted / Kabul tarihi:*** *06.10.2008*

Objectives: The aim of our study was to compare the efficacy of hyperbaric and isobaric solutions of intrathecal levobupivacaine for transurethral endoscopic surgery.

Patients and Methods: The study included urological patients who were scheduled for elective surgery under spinal anesthesia. The cases were randomly divided into three groups of 20 patients each. Group 1 received 13.5 mg hyperbaric levobupivacaine, group 2 received 12.5 mg isobaric levobupivacaine and group 3 received 15 mg isobaric levobupivacaine in a total volume of 3 ml intrathecally. Sensory and motor block, hemodynamic parameters, pain scores, adverse effects and analgesic requirements of the patients were recorded.

Results: The time to reach T10 sensory block and the onset time to Bromage 0 were statistically different among the three groups ($p<0.05$). The mean time to reach T10 was significantly lower in group 1 when compared with group 2 ($p<0.001$). Regarding the mean onset time to Bromage 0, group 1 had a lower mean value than that of group 3 ($p<0.001$). The mean duration for analgesic requirement was longer in group 1 than in groups 2 and 3 ($p<0.001$ and $p<0.05$, respectively).

Conclusion: We concluded that the clinical efficacy of hyperbaric levobupivacaine was superior to the isobaric forms in spinal anesthesia for transurethral endoscopic surgery.

Key words: Intrathecal; levobupivacaine; analgesia; anesthesia.

Amaç: Bu çalışmanın amacı transüretral endoskopik cerrahide intratekal izobarik ve hiperbarik levobupivakainin etkinliğini kıyaslamaktır.

Hastalar ve Yöntemler: Çalışmaya, spinal anestezi altında elektif ürolojik cerrahi planlanan olgular alındı. Olgular rastgele 20 hastadan oluşan üç gruba ayrıldı. İntratekal yolla toplamda 3'er ml, Grup 1 olgulara (n=20) 13.5 mg hiperbarik levobupivakain, Grup 2 olgulara (n=20) 12.5 mg izobarik levobupivakain ve Grup 3 olgulara (n=20) 15 mg izobarik levobupivakain uygulandı. Tüm olgularda duyusal ve motor blok, hemodinamik parametreler, ağrı skorları, yan etkiler ve analjezik gereksinimler kaydedildi.

Bulgular: Ortalama T10 duyusal blok ve Bromage 0'a ulaşma süreleri açısından gruplar arası farklılık saptandı ($p<0.05$). Grup 2 ile kıyaslandığında Grup 1'de T10'a ulaşma süresi belirgin bir şekilde daha düşüktü ($p<0.001$). Motor bloğun kalkması (Bromage 0 düzeyine erişme süreleri) için geçen süre Grup 1'de Grup 3'ten daha düşük değere sahipti ($p<0.001$). Ameliyat sonrası ilk analjezik gereksinimi için geçen süre Grup 1'de Grup 2 ve 3'ten daha uzun bulundu (sırasıyla $p<0.05$ ve $p<0.001$).

Sonuç: Transüretral endoskopik cerrahi için yapılan spinal anestezide hiperbarik form levobupivakainin klinik etkisinin, izobarik formlardan daha etkin olduğu sonucuna vardık.

Anahtar sözcükler: İntratekal; levobupivakain; analjezi; anestezi.

Correspondence (İletişim adresi): Dr. Hüseyin Şen. GATA Haydarpaşa Eğitim Hastanesi, Anestezi ve Reanimasyon Servisi, 34668 İstanbul.
Tel: 0216 - 542 20 20 Fax (Faks): 0216 - 348 78 80 e-mail (e-posta): drhuseyinsen@hotmail.com

Concerns about bupivacaine's adverse cardiac effects motivated researchers to develop new, safer compounds. In this regard, (S-) bupivacaine (levobupivacaine) has been recognized to have less cardiovascular and central nervous system toxicity.[1,2] Therefore, levobupivacaine administered via the epidural route has the advantage of less cardiotoxicity should accidental intravascular injection occur.[3] The currently available data on levobupivacaine and racemic bupivacaine for epidural anesthesia, brachial plexus blocks and local infiltration show a similar analgesic potency whereas levobupivacaine tends to induce more sustained sensory and motor blocks.[4-10] Despite several side effects of regional techniques, in elderly patients with high cardiac risk, they may be preferred to general anesthesia due to better hemodynamic stability.[11-12]

To our best notice, there is no study that has investigated different doses of hyperbaric levobupivacaine for spinal anesthesia. This prompted us to compare the effects of intrathecal hyperbaric and isobaric solutions of levobupivacaine in a group of male patients –who had underwent transurethral endoscopic surgery– in a prospective, randomized, double-blinded study.

PATIENTS AND METHODS

After approval by the Ethical Committee for Research in Human Subjects, urological male patients aged ≤85 years (physical status I-III according to American Society of Anesthesiologists (ASA)) who were scheduled for elective transurethral endoscopic surgery under spinal anesthesia were enrolled in the present prospective, randomized, double-blind study. Written informed consent was obtained from all patients. Patients with known hypersensitivity to amide local anesthetics, coagulopathy, height of less than 145 cm, or weight of more than 100 kg were excluded.

The patients were randomly allocated to three groups by using a computer: Group 1 (n=20) received 13.5 mg hyperbaric levobupivacaine, Group 2 (n=20) received 12.5 mg isobaric levobupivacaine and Group 3 (n=20) received 15 mg isobaric levobupivacaine. All individuals were given the aforementioned doses within a volume of 3 ml intrathecally. Hyperbaric levobupivacaine solutions comprised 3 ml of levobupivacaine, 7.5 mg/ml^{-1} (Chirocaine, Abbott) plus 2 ml of dextrose 200 mg/ml^{-1}.

None of the patients received premedications and other drugs that the patients had to use were continued until the operating day. In the operating room, all of the patients had both legs wrapped with an elastic bandage to prevent hypotension. Subjects were monitorized with non-invasive blood pressure, pulse oxygen (SpO_2), and electrocardiography evaluations (Datex Ohmeda S/5 Helsinki/Finland). After 6 ml/kg of 0.9% saline infusion for one hour, intrathecal administration of levobupivacaine was performed under aseptic conditions and with the patients in sitting position. Infiltration was done by using a 24-gauge Quincke needle with a midline approach at L3-4 slowly (at least 10 seconds) without Barbotage's technique by the same anesthesiologist who was blind to the type of local anesthetic. The surgical procedure was started 20 min after initiation of the spinal anesthesia, as soon as the analgesic level at T10 was established. Intraoperatively, the patients received 2 ml/kg/hr 0.9% saline solution.

Immediately after administration, the patients were turned into a supine position with a pillow under their head. Oxygen (2-3 L/min) was given via a mask. Standard monitoring was continued throughout the operation. Sensory blockade was assessed by using pinprick test on each side of the midclavicular line, motor blockade was assessed based on a modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, and 3 = inability to flex ankle joints). These tests were performed on the 1st, 3rd, 5th min, every 5 min up to the 30th min and every 10 min until the end of the operation. Postoperatively, the testing was done on the 5th, 10th min and every 10 min until the sensory and motor variables became normal. Postoperative quality of anal-

Table 1. Demographic and clinical features of the patients

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p*
Age (year)	72 (21-84)	69 (24-83)	69 (21-84)	0.789*
Weight (kg)	75.00±5.53	76.50±9.41	73.80±7.03	0.524**
Height (cm)	173.00±5.53	173.20±5.18	171.20±4.02	0.379**
Operation time (min)	57.5 (20-110)	55 (15-130)	56.75 (15-100)	0.611*
BMI (kg/m^2)	24.99 (22.04-28.34)	24.41 (21.22-38.39)	25.47 (21.34-36.06)	0.528*
ASA (I/II-III)	9/11	7/13	4/16	0.465***
TUR (p/b/ed)	12/8/0	10/7/3	10/10/0	0.146***

* Kruskal-Wallis test [median(min-max)]; ** ANOVA test (mean±standard deviation); *** Chi-Square test
BMI: Body mass index; ASA: American Society of Anesthesiologists; TUR: Transurethral resection (p, prostate; b, bladder; ed, ejaculation duct)

gesia was evaluated with visual analogue scale (VAS) –from 0 to 10 where 0 defines no pain and 10 defines the worst pain ever suffered– every hour until VAS≥4. Patients who had a VAS score ≥4 were given i.m. 75 mg diclofenac and the time of analgesic administration was recorded as the time for postoperative analgesic requirement.

The hemodynamic variables and SpO_2 were recorded one hour before spinal anesthesia (immediately before the saline infusion) and on the 1st, 3rd, 5th min, every 5 min up to the 30th min and every 10 min until the end of the operation. Postoperatively, monitorization was performed on the 5th, 10th min and every 10 min for 90 min. Hypotension was defined as a decrease in systolic blood pressure either >25% from baseline, or less than 90 mmHg; and it was treated with intravenous (IV) ephedrine 5 mg. Bradycardia was defined as a heart rate <45 bpm and it was treated with IV atropine 0.5 mg. Nausea-vomiting were recorded and metoclopramide 10 mg IV was administered for treatment. If needed, (according to Ramsey sedation scale) supplementary sedation was provided with 2 mg IV midazolam.

Statistical Package for Social Sciences was used for statistical analysis. According to the distribution of the data; Kruskal-Wallis, Mann-Whitney U-test, ANOVA and chi-square tests were performed and the priori level of significance was set at $p<0.05$.

Table 2. Hemodynamic parameters of the patients

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p**
MBP (basal)	110.75±13.92	106.20±18.29	112.30±10.60	0.396
MBP (5th min)	103,85±13.38	104.45±19.19	104.75±16.08	0.984
MBP (10th min)	104.25±13.96	103.80±18.23	103.15±16.37	0.977
MBP (15th min)	99.55±13.95	102.45±17.67	101.55±15.59	0.839
MBP (30th min)	99.62±12.14	98.46±15.11	100.94±14.79	0.890
MBP postoperative (10th min)	90.84±16.61	87.65±11.85	94.30±12.23	0.328
MBP postoperative (30th min)	91.71± 9.96	89.12±14.18	94.00±10.03	0.506
HR (basal)	80.25±17.70	76.95±21.31	73.85±12.89	0.522
HR (5th min)	80.25±17.04	75.20±16.40	69.85±14.49	0.131
HR (10th min)	76.45±15.78	74.30±19.32	66.50±10.88	0.263
HR (15th min)	72.60±14.36	71.70±15.36	65.45±9.29	0.188
HR (30th min)	69.41±14.40	73.92±13.80	63.47±12.60	0.119
HR postoperative (10th min)	71.23±15.47	66.94±11.71	64.45±9.13	0.287
HR postoperative (30th min)	68.86±15.72	69.63±12.90	64.52±15.35	0.577

* ANOVA test (mean±standard deviation); MBP: Mean blood pressure; HR: Heart rate.

Table 3. Distribution of highest levels of sensory block

	T4	T5	T6	T7	T8	T10
Group 1	1	0	8	1	1	9
Group 2	0	0	5	0	1	14
Group 3	1	1	4	1	1	12

RESULTS

Demographic and clinical features of the patients are given in Table 1. Intraoperative and postoperative blood pressure, heart rate, SpO_2 values were found to be statistically similar ($p>0.05$) (Table 2).

The distribution of highest levels of sensory block is shown in Table 3. Comparison of sensory and motor block is given in Table 4. The time to reach T10 sensory block and the time to the onset of Bromage 0 were statistically different among the three groups ($p< 0.05$). The mean time to reach T10 was significantly lower in group 1 when compared with group 2 ($p<0.001$). The rest of the individual comparisons between groups yielded statistically similar results. Regarding the mean onset time to Bromage 0, the only statistical significance was between groups 1 and 3, whereas group 1 had a lower mean value than that of group 3 ($p<0.001$).

Mean duration of initial analgesic requirement was statistically different among the three groups ($p<0.001$). It was longer in group 1 than in groups 2 and 3 ($p<0.001$ and $p<0.05$, respectively) (Table 4).

Postoperative VAS values were statistically indifferent among groups at any time of measurement ($p>0.05$).

Adverse events were infrequent and minor; bradycardia was seen in two patients in group 1 and in three patients in group 3. Hypotension was observed in two patients in groups 1 and 3 and in one patient in group 2. There was only one patient who had nausea and vomiting in group 3. These patients were treated as mentioned above. Sedation with midazolam was given in two patients in group 2.

DISCUSSION

In this study, three different doses of levobupivacaine was compared with respect to hemodynamic effects, sensory and motor block. The two main findings were that the onset time to reach T10 sensory block and the time to recover from motor block were significantly less with hyperbaric levobupivacaine.

After its cardiotoxic and central nervous system depressant effects were found to be less when compared with bupivacaine, several studies have been conducted on levobupivacaine. Alley et al.[8] performed a randomized, double-blind, cross-over study in healthy volunteers to compare 0.25% hyperbaric levobupivacaine and racemic bupivacaine for spinal anaesthesia. Sensory and motor block were similar between the same doses of levobupivacaine and bupivacaine, and hyperbaric spinal levobupivacaine had equivalent clinical efficacy to racemic bupivacaine for spinal anesthesia in doses from 4

Table 4. Comparison of follow up parameters among groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p*
The onset time of T10 sensory block (min)	4.50 (1-16)	10 (3-20)	5 (3-20)	0.002*
Time to two segment regression of sensory block (min)	32.5 (5-95)	25 (5-100)	32.5-10-100)	0.969*
Time to maximum sensory block (min)	7.5 (3-40)	12.5 (3-60)	7.5 (3-70)	0.345*
Regression to L1 (min)	70 (30-120)	75 (15-150)	80 (30-140)	0.830*
Time to motor block Bromage 1 (min)	3 (1-10)	5 (1-20)	3 (1-19)	0.211*
Time to motor block Bromage 3 (min)	10 (3-25)	15 (3-30)	10 (3-40)	0.117*
Time to motor block Bromage 0 (min)	67.5 (20-140)	82.5 (35-160)	110 (60-170)	0.011*
Initial analgesic requirement time (hour)	9.90±1.52	6.45±0.99	7.15±0.88	<0.001**

* Kruskal-Wallis test [median(min-max)]; ** ANOVA test (mean±standard deviation)

to 12 mg. Similarly, Glaser et al.[7] found that intrathecal levobupivacaine was equal in efficacy to, but less toxic than, racemic bupivacaine in patients undergoing elective hip replacement. Vercauteren et al.[9] found that levobupivacaine had less motor impairment when compared with racemic bupivacaine in intrathecal labor analgesia. The study of Vanna et al.[10] demonstrated that 2.5 ml of 0.5% isobaric levobupivacaine and 0.5% hyperbaric of racemic bupivacaine showed equally effective potencies for spinal anesthesia in TUR surgery regarding the onset time and duration of sensory blockade. In another study, Lee et al.[6] compared the efficacy of 2.6 ml of an isobaric solution of 0.5% levobupivacaine with 0.5% racemic bupivacaine again in TUR surgery and they observed that there were no significant differences in quality of sensory and motor block or hemodynamic change.

Although different doses of levobupivacaine have not been studied, Lee et al.[13] compared levobupivacaine vs levobupivacaine combined with fentanyl. They have found that 2.3 mL of 0.5% levobupivacaine with fentanyl 15 μg was as effective as 2.6 mL of 0.5% levobupivacaine alone in spinal anaesthesia for TUR surgery.

In our study, we compared the three different doses of levobubivacaine (13.5 mg hyperbaric, 12.5 mg, 15 mg in 3 ml volume) with respect to clinical efficacy and adverse effects. We observed that the time to two segment regression of sensory block, time to maximum sensory block, time to regression to L1, time to motor block Bromage 1 and 3 were similar. On the other hand, we found that the time to reach T10 was significantly lower with hyperbaric levobupivacaine (13.5 mg) when compared with isobaric form (12.5 mg). Although statistically not significant, hyperbaric group also had T10 sensory block earlier than group 3 (isobaric 15 mg). When the onset time to Bromage 0 was considered, it was lower in the hyperbaric group in comparison with the isobaric group (15 mg). Again although not significant, hyperbaric group had onset of Bromage 0 earlier than isobaric group (12.5). Hemodynamic parameters, VAS scores and adverse effects seemed to be similar among groups but mean duration for analgesic requirement was longer in the hyperbaric group than the other two groups.

In conclusion, our first and preliminary results showed that the clinical efficacy of hyperbaric levobupivacaine was superior to the isobaric forms in spinal anesthesia during TUR surgery. Keeping in mind the fact that outpatient spinal anesthesia is increasingly being performed in daily practice; drugs that provide early recovery from motor block and less postoperative analgesic requirement are of quite interest. In this regard, further studies are needed to evaluate different forms of levobupivacaine or its combinations with other adjuvant drugs in other types of surgeries.

REFERENCES

1. Gristwood RW. Cardiac and CNS toxicity of levobupivacaine: strengths of evidence for advantage over bupivacaine. Drug Saf 2002;25:153-63.
2. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol 1998;46:245-9.
3. Kopacz DJ, Allen HW. Accidental intravenous levobupivacaine. Anesth Analg 1999;89:1027-9.
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;80:594-8.
5. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LM. Extradural S(-)-bupivacaine: comparison with racemic RS-bupivacaine. Br J Anaesth 1998;80:289-93.
6. Lee YY, Muchhal K, Chan CK. Levobupivacaine versus racemic bupivacaine in spinal anaesthesia for urological surgery. Anaesth Intensive Care 2003;31:637-41.
7. Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg 2002;94:194-8.
8. Alley EA, Kopacz DJ, McDonald SB, Liu SS. Hyperbaric spinal levobupivacaine: a comparison to racemic bupivacaine in volunteers. Anesth Analg 2002;94:188-93.
9. Vercauteren MP, Hans G, De Decker K, Adriaensen HA. Levobupivacaine combined with sufentanil and epinephrine for intrathecal labor analgesia: a comparison with racemic bupivacaine. Anesth Analg 2001;93:996-1000.
10. Vanna O, Chumsang L, Thongmee S. Levobupivacaine and bupivacaine in spinal anesthesia for tran-

surethral endoscopic surgery. J Med Assoc Thai 2006;89:1133-9.
11. Turan A, Kaya G, Öztürk N, Pamukçu Z. Spinal anestezi uygulanan bir olguda antidepresan kullanımına bağlı konvulsiyon. Trakya Univ Tıp Fak Derg 2003;20:43-6.
12. Çolak A, İnal MT, Arar C, Oğuzhan N, Pamukçu Z. Yüksek kardiyak riskli hastada sürekli spinal anestezi uygulaması. Trakya Univ Tıp Fak Derg 2007;24:150-2.
13. Lee YY, Muchhal K, Chan CK, Cheung AS. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. Eur J Anaesthesiol 2005;22:899-903.