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Intrathecal Bupivacaine in Humans

Influence of Volume and Baricity of Solutions

Jean-Marc Malinovsky, M.D., Géraldine Renaud, M.D.,† Pascal Le Corre, Pharm.D., Ph.D.,‡ Florence Charles, M.D.,† Jean-Yves Lepage, M.D.,* Myriam Malinge, M.D., Ph.D.,* Antoine Cozian, M.D.,* Olivier Bouchot, M.D.,§ Michel Pinaud, M.D.‖*

Background: **The effects of volume and baricity of spinal bupivacaine on block onset, height, duration, and hemodynamics were studied.**

Methods: **Ninety patients undergoing endoscopic urologic procedures were randomized to receive 10 mg of intrathecal bupivacaine at L2–L3 level in sitting position. In the operating room, commercial products were diluted as needed with NaCl 0.9% to obtain isobaric solutions (density, 1.005–1.008) or with NaCl 0.9% and glucose 30% to obtain hyperbaric solutions (density, 1.031–1.037) of 2, 5, or 10 ml (six groups of 15 patients each). Three minutes after spinal injection the patients were placed in lithotomy position. Sensory blockade was assessed using pinprick and cold sensation tests, and motor blockade was assessed using a four-point scale.**

Results: **Onset times to maximal cephalad spread of spinal blockade were similar with isobaric and hyperbaric solutions. A greater maximal cephalad spread of anesthesia was obtained with diluted isobaric bupivacaine but was not associated with more hypotension. Volume had no effect on cephalad extent of anesthesia with hyperbaric bupivacaine. Times for regression of anesthesia to L2 and offset of motor block were longer with isobaric than with hyperbaric solutions of bupivacaine. The intensity of motor blockade was decreased with diluted hyperbaric bupivacaine. No patient reported back pain.**

Conclusion: **In this study, volume had no significant influence on either cephalad spread or duration of sensory blockade for either isobaric or hyperbaric bupivacaine. Time for offset of anesthesia was shorter with hyperbaric bupivacaine compared with isobaric solutions. (Key words: Local anesthetics; spinal anesthesia.)**

THE duration of spinal anesthesia is related to the dose of hyperbaric[1-3] or isobaric bupivacaine administered.[4-6] The relationship between volume, dose, and concentration of intrathecal local anesthetics and the sensory spread of anesthesia has been extensively studied using isobaric local anesthetics. However, the impact of injected volume on the spread of sensory blockade with bupivacaine is not clear. Some authors have found no difference in the spread of anesthesia when the volume of injectate was more than 3 ml.[7-9] In contrast, a small volume (2 ml) of 0.75% bupivacaine resulted in a shorter cephalad spread of anesthesia.[10,11] Using hyperbaric tetracaine, the volume did not modify the cephalad spread of anesthesia (volumes ranging from 1 to 4 ml),[12] but this relationship has not been yet reported with hyperbaric bupivacaine.

The use of large volume of injectate solutions is not frequently done intrathecally.[13] It is noteworthy that volumes of local anesthetic solutions ranged from 1 to 6 ml in many available studies, these volumes being small compared with the quantity of cerebrospinal fluid (CSF) surrounding the lumbar spinal cord.[14] Moreover, the use of concentrated solutions in volumes up to 10 ml of bupivacaine as isobaric compared with hyperbaric solutions has not been done to date. Therefore, we designed a study to determine the relationship between the volume and baricity of bupivacaine and the time-course of sensory and motor blockades in surgical patients.

Materials and Methods

After approval by our local research committee and the regional ethics committee, 90 patients with American Society of Anesthesiologists physical status I–III and

* Anesthesiologist.

† Resident in Anesthesiology.

‡ Assistant Professor of Biopharmaceutics.

§ Professor of Urology.

‖ Professor of Anesthesiology and Department Head.

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Address reprint requests to Dr. Malinovsky: Department of Anesthesiology, Hôtel-Dieu, 44093 Nantes Cedex 1, France. Address electronic mail to: jmmalino@sante.univ-nantes.fr

Table 1. Characteristics of Intrathecally Injected Bupivacaine Solutions at a Temperature of 25°C (N = 15 Samples of Each Solution)

Volume (ml)	0.5% Bupivacaine (ml)	NaCl 0.9% (ml)	Glucose 30% (ml)	Total (ml)	*p*H	Density	Osmolarity (mOsm/l)
Hyperbaric							
2	2	—	—	2	6.0	1.031 ± .003	481 ± 12
5	2	1.5	1.5	5	6.0	1.036 ± .002	741 ± 31
10	2	5	3	10	6.0	1.037 ± .003	772 ± 38
Isobaric							
2	2	—	—	2	6.5	1.008 ± .002	289 ± 7
5	2	3	—	5	6.5	1.006 ± .002	285 ± 5
10	2	7	—	10	6.5	1.005 ± .003	288 ± 8

Values are mean ± SD. Solutions were prepared from commercial bupivacaine solution (Marcaïne; Astra Laboratories, Rueil Malmaison, France).

a healthy body mass index were included in this randomized, double-blind study after giving their informed written consent. They were scheduled for endoscopic resection of the bladder or prostate or urethral surgery with spinal anesthesia.

Premedication consisted of 10 mg of oral midazolam and prophylactic antibiotics. Patients received no vascular loading before administration of spinal anesthesia. They were monitored by electrocardiography and an automatic blood pressure cuff. Intrathecal bupivacaine injection was performed in the operating room using a 27-gauge needle at the L2–L3 level with the patient in sitting position. Patients were randomly assigned to one of six groups, each receiving 10 mg of intrathecal bupivacaine:

2 ml of isobaric bupivacaine (0.5%);
5 ml of isobaric bupivacaine (0.2%);
10 ml of isobaric bupivacaine (0.1%);
2 ml of hyperbaric bupivacaine (0.5%);
5 ml of hyperbaric bupivacaine (0.2%);
or 10 ml of hyperbaric bupivacaine (0.1%).

Isobaric bupivacaine solutions were prepared in the operating room using 2 ml of 0.5% bupivacaine (Marcaïne, Astra Laboratories, Rueil Malmaison, France) diluted with NaCl 0.9% as needed to obtain a total volume of 5 or 10 ml. Hyperbaric bupivacaine solutions were prepared using 2 ml of 0.5% hyperbaric bupivacaine containing 7% glucose (Marcaïne®) diluted with NaCl 0.9% and glucose 30% as needed to obtain solutions containing 7% glucose in either 5 or 10 ml. The composition and physicochemical properties of each solution are reported in table 1.

Intrathecal injections were performed during a 30-s period in all groups. After injection patients were placed in lithotomy position with no elevation of the torso in a mean time of 3 min after the injection (range, 2–4 min). Then patients were tested every 3 min up to the maximal spread of blockades and then every 10 min until recovery of L2. Spinal injection was always performed by a physician other than those who monitored anesthesia.

Sensory blockade was assessed using pinprick and cold sensation (iced tube) tests on each side of the midclavicular line. The degree of motor blockade was scored from 0 to 3: 0 = no motor effects; 1 = a decrease in muscle strength with ability to move the leg against pressure; 2 = inability to move the leg against pressure without complete paralysis; and 3 = complete paralysis of extension at the knee. Onset time for blockade was defined as the time between injection and maximal blockade. Block duration was defined as the period between injection and recovery from blockade (L2 for sensory blockade and total recovery from motor effects).

Mean arterial blood pressure (MAP) was recorded every 3 min throughout the study and surgery. When MAP decreased more than 25% from the baseline value, patients received boluses of intravenous ephedrine, 3 mg, every 3 min up to a total dose of 9 mg. Thereafter patients received vascular loading, using crystalloid solution. Patients who required fluids and vasopressors were considered to have had hypotension. A decrease in heart rate below 40 beats/min was managed with 0.01 mg/kg of intravenous atropine.

The density, pH, and osmolarity of injected bupivacaine solutions were measured using a densitometer (Refractometer Atago Co., Tokyo, Japan), a pH meter (P12, Beckman, Brea, CA), and an osmometer (3MO Plus, Advanced Instruments Inc., Norwood, MA).

Every day during the first 5 postoperative days and then 1 month later patients were asked about back pain radiating into the legs and buttocks.

Table 2. Demographic Data and Duration of Surgical Procedures

	Isobaric Bupivacaine			Hyperbaric Bupivacaine		
	2 ml	5 ml	10 ml	2 ml	5 ml	10 ml
Age (yr)	68 ± 11	66 ± 10	70 ± 8	73 ± 7	70 ± 10	70 ± 10
Height (cm)	170 ± 5	163 ± 9	169 ± 9	172 ± 6	173 ± 8	166 ± 8
Weight (kg)	73 ± 8	70 ± 10	70 ± 8	77 ± 5	75 ± 9	68 ± 10
Duration of surgery (min)	51 ± 33	42 ± 36	34 ± 20	32 ± 33	37 ± 23	37 ± 24

Values are mean ± SD. All comparisons are not statistically significant.

Statistics

The size of the sample was based on the results of a pilot study, and the intention was to show a significant difference in spread of anesthesia of 2 or 3 dermatomes with a SD of 2 dermatomes, with an α risk at 0.05 and a β risk at 0.20. Comparisons between groups for onset time of sensory and motor blockades and cephalad spread of sensory blocks were performed using Kruskal-Wallis and Mann-Whitney tests. The ability to obtain a complete motor blockade was compared using a contingency table between isobaric and hyperbaric solutions. MAP changes were compared using analysis of variance (ANOVA) for repeated measurements; ephedrine and crystalloid requirements and frequency of hypotension were compared using a contingency table. The significance level was set at $P < 0.05$.

Results

Demographic data are summarized in table 2. One patient in the group receiving 5 ml of isobaric bupivacaine required general anesthesia and was excluded from analysis. The surgical procedure was performed without pain in the 89 remaining patients. No patient reported back pain during 4 weeks of follow-up evaluation.

The volume of isobaric bupivacaine had no influence on the onset time or on the total duration of sensory blockade (table 3 and figs. 1 and 2). Results showed the upper level of the cold sensation test was always higher than that of the pinprick test (fig. 3). The maximal cephalad spread of block was also higher after administration of 10 ml than after 2 ml (pinprick sensation only) and 5 ml (pinprick and cold sensation; fig. 3). Onset time and total duration of motor blockade were not modified by volume. The incidence of complete paralysis of leg extension was the same, regardless of the volume injected (fig. 4). Heart rate did not change significantly in any group, and no patient experienced bradycardia. Hypotensive episodes requiring intervention with ephedrine and crystalloids were more frequent with patients receiving 2 ml than in those receiving larger volumes of isobaric bupivacaine (10 ml [2 patients of 15], 5 ml [3 patients], and 2 ml [9 patients]; $P < 0.01$).

The volume of hyperbaric bupivacaine had no influence on the onset time or on the total duration of sensory blockade (table 4 and figs. 1 and 2). The maximal cephalad spread of anesthesia was not modified by volume, but was higher for all volumes when determined by loss of cold sensation than by pinprick test (fig. 3). More patients in the 2-ml group experienced complete paralysis than in the 5-ml group ($P < 0.05$; fig. 4). Heart rate did not change significantly in any group, and no patient experienced bradycardia. Hypotensive episodes requiring the use of ephedrine and crystalloids were not statistically different among the groups (10 ml

Table 3. Onset Time (Time between Injection and Maximal Blockade) and Total Duration of Complete Recovery from Pinprick and Cold Sensory Blockades (Time between Injection and Recovery to L_2) and of Complete Recovery from Motor Blockade (Time between Injection and Complete Offset of Motor Blockade) after 10 mg of Isobaric Bupivacaine

Volume (ml)	Onset Time (min)			Total Duration (min)		
	Pinprick	Cold	Motor	Pinprick	Cold	Motor
2	10 (3–29)	10 (3–20)	13 (4–22)	122 (35–250)	140 (65–260)	175 (50–250)
5	15 (6–34)	16 (6–30)	18 (4–44)	142 (60–240)	180 (70–240)	204 (50–260)
10	13 (4–37)	14 (4–33)	18 (6–53)	160 (50–267)	180 (80–300)	177 (77–280)

Values are median (range). All comparisons are not statistically significant.

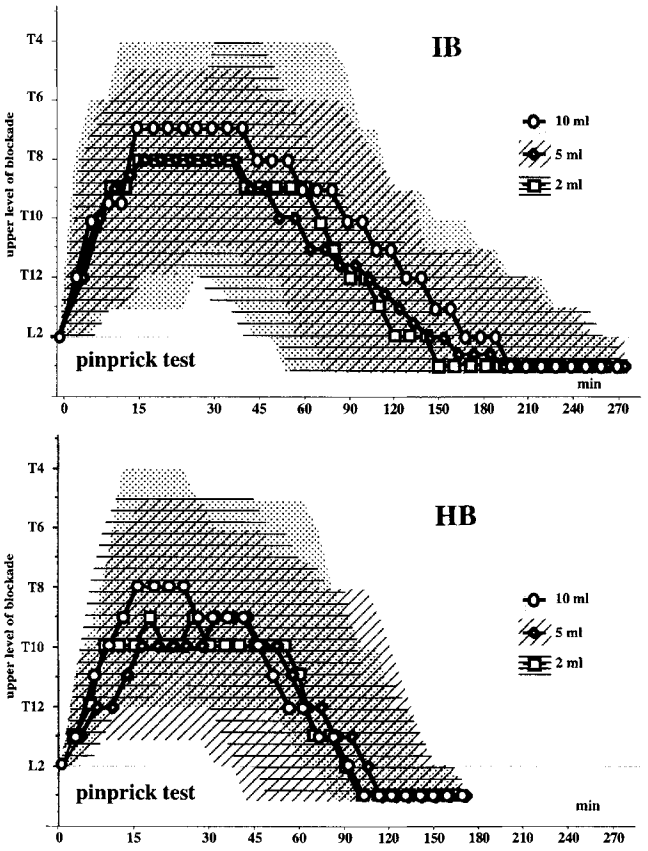

Fig. 1. Changes in the median upper level of pinprick blockade with time in patients receiving 10 mg of intrathecal isobaric (IB, *upper panel*) or hyperbaric (HB, *lower panel*) bupivacaine. Areas represent the range observed in each group (filled with horizontal bars for the 2-ml group; with diagonal bars for the 5-ml group, and grey for the 10-ml group). The duration of pinprick blockades was not modified by the volume of IB and HB bupivacaine. The duration of pinprick block was longer with IB than with HB solutions.

[five patients], 5 ml [two patients], and 2 ml [three patients]).

The onset time of sensory blockade was the same for isobaric and hyperbaric bupivacaine. The total duration of sensory blockade was significantly longer for isobaric than hyperbaric solutions for the 5-ml ($P < 0.01$ for the pinprick test and $P < 0.05$ for the cold sensation test) and 10-ml groups ($P < 0.01$ for the pinprick and cold sensation tests; tables 3 and 4). For larger volumes (5 and 10 ml) onset time of motor blockade was longer with isobaric than with hyperbaric bupivacaine ($P < 0.05$), and more patients experienced complete paralysis of the knee in isobaric group than in hyperbaric groups ($P < 0.01$). The duration of motor blockade was shorter after administration of hyperbaric than after that of isobaric bupivacaine, regardless of the volume injected ($P < 0.01$).

Discussion

Our results demonstrate a longer recovery time from anesthesia and greater motor blockades with isobaric than with hyperbaric bupivacaine. They also confirm those of Gaggero *et al.*[12] with respect to hyperbaric solutions, which showed no effects of volume on cephalad extent of anesthesia.

It has been reported that spinal anesthesia with 0.10% bupivacaine is inadequate to achieve surgical anesthe-

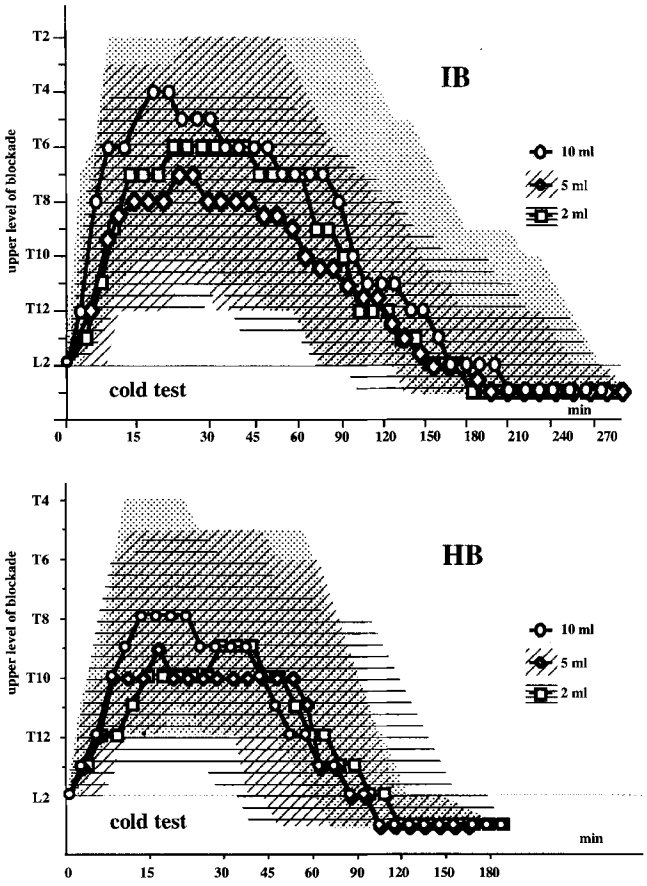

Fig. 2. Changes in the median (range) upper level of cold sensation blockade with time in patients receiving 10 mg of intrathecal isobaric (IB, *upper panel*) or hyperbaric (HB, *lower panel*) bupivacaine. Areas represent the range observed in each group (filled with horizontal bars for the 2-ml group; with diagonal bars for the 5-ml group, and grey for the 10-ml group). The time course and duration of cold sensation blockades were not modified by the volume of IB and HB bupivacaine. The duration of cold sensation block was longer with IB than with HB solutions.

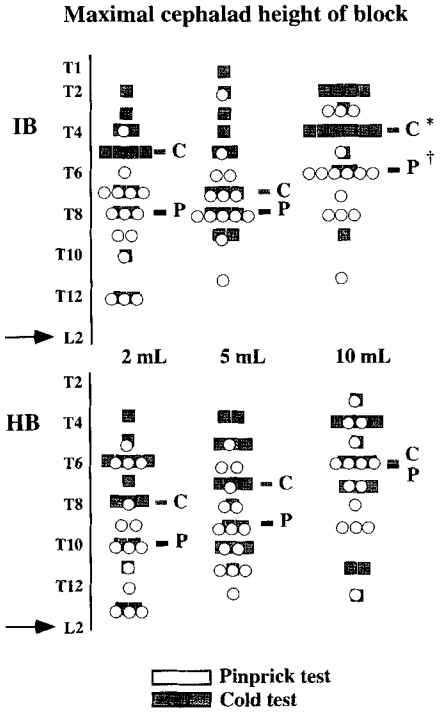

Fig. 3. Spread of anesthesia with 10 mg of bupivacaine as isobaric or hyperbaric solution. Each point represents individual data for pinprick blockade level or cold sensation blockade level. The median level in each group is represented by the solid bar (P = pinprick; C = cold sensation). †$P < 0.05$ *vs.* 2 ml and *$P < 0.05$ *vs.* 5 ml.

sia.[3,15] However, the absolute dose would appear to be a more important factor than either the volume of solution or concentration of agent because low doses (5 mg or less) were associated with inadequate surgical anesthesia in some cases,[3,15] whereas a dose of 8 mg[15] or higher reliably provided surgical anesthesia. In our series, 10 mg of bupivacaine provided surgical anesthesia with either isobaric or hyperbaric solutions regardless of injectate volume (or concentration).

Given that the level of blockade increased as the volume of isobaric bupivacaine increased, one might have suspected an association between injected volume and the incidence of hypotension. Surprisingly, the hypotensive episodes requiring intervention with ephedrine and crystalloids were more frequent in patients who received 2 ml than in those who received larger volumes of isobaric bupivacaine. We hypothesized that as the concentration of the injected solution decreases, the concentration of bupivacaine penetrating the nerve is lower, thus reducing the degree of sympathetic blockade. Sympathetic blockade was not determined directly in our study, although the skin vasomotor reflex, which is controlled by sympathetic vasomotor neurons and appears to be an objective indicator of the level of spinal anesthesia, correlates with cold sensation level.[16] In the present study, cold sensations were blocked around the T7 level with administration of 2 ml solution and around the T6 level with 10 ml. The fact that sensory blockade in all groups was more cephalad with respect to cold than to pinprick sensations may relate to the diameter of the transmitting fibers, which is smaller for cold sensation than for pinprick stimulations.

For isobaric and hyperbaric solutions there was no influence of increasing injectate volume on the time course of the blockade. However, for hyperbaric bupivacaine the more concentrated, low volume inject-

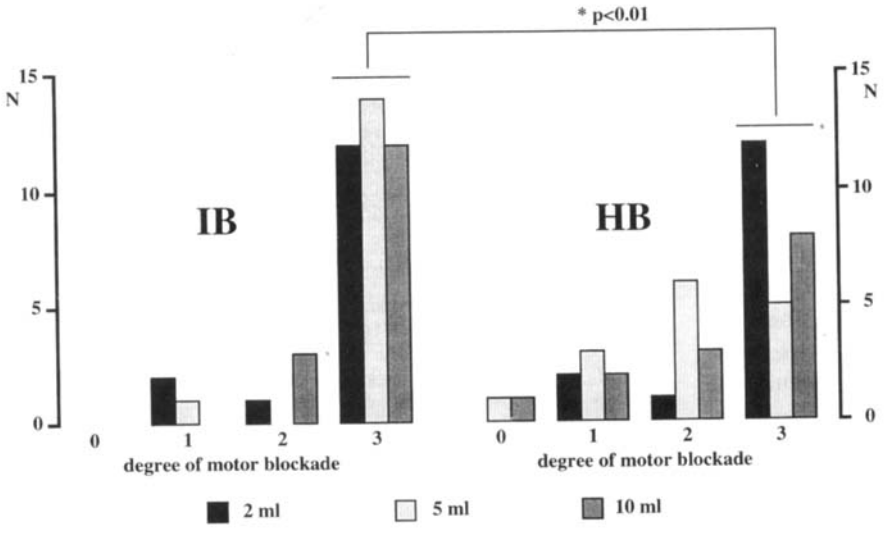

Fig. 4. The intensity of motor effects after intrathecal administration of 10 mg bupivacaine as an isobaric (IB; *left panel*) or hyperbaric (HB; *right panel*) solution. N represents the number of patients who reached the different levels of motor blockade. The degree of motor blockade was scored from 0 to 3: 0 = no motor effects; 1 = a decrease in muscle strength, with ability to move the leg against pressure; 2 = inability to move the leg against pressure without complete paralysis; and 3 = complete paralysis of extension at the knee. Complete motor blockade was experienced by more patients receiving isobaric than hyperbaric bupivacaine (*$P < 0.01$).

Table 4. Onset Time (Time between Injection and Maximal Blockade) and Total Duration of Complete Recovery from Pinprick and Cold Sensory Blockades (Time between Injection and Recovery to L_2) and of Complete Recovery from Motor Blockade (Time between Injection and Complete Offset of Motor Blockade) after 10 mg of Hyperbaric Bupivacaine

Volume (ml)	Onset Time (min)			Total Duration (min)		
	Pinprick	Cold	Motor	Pinprick	Cold	Motor
2	15 (3–35)	11 (4–31)	15 (−24)	97 (35–170)	117 (40–185)	120 (40–290)
5	14 (6–26)	13 (4–30)	13 (3–20)	88 (40–180)	96 (40–180)	95 (55–220)
10	13 (6–43)	13 (3–43)	9 (2–22)	87 (55–145)	115 (70–150)	92 (70–175)

Values are median (range). All comparisons are not statistically significant.

ate yielded a more intense motor block compared with large volume of low concentrated solution. This difference disappeared using isobaric bupivacaine. Addition of glucose to bupivacaine increases the density of the solution and may alter the local anesthetic diffusion in CSF. We speculate that an increase in injected volume led to a reduced amount of hyperbaric bupivacaine available to block motor fibers, which are in an anterior position in patients positioned supine. However, when higher doses of hyperbaric bupivacaine are injected the difference in terms of motor effects disappears.[17]

Since the reporting of transient or permanent cauda equina syndrome, the use of lidocaine with spinal anesthesia has been questioned.[18,19] As an alternative to lidocaine, some authors have proposed the use of small doses of bupivacaine, especially with administration of ambulatory anesthesia.[3,15] Our results indicate that a hyperbaric solution induced shorter anesthesia and motor blockade than an isobaric solution, a point that should be useful in adapting bupivacaine spinal anesthesia to the ambulatory setting.

The interindividual variations in effects with use of intrathecal bupivacaine have been emphasized.[11] The large variations in onset time and total duration of the sensory blockade may have been partially a result of large variations in volume of CSF around the spinal cord. It has been demonstrated that this volume can range from 25 to 80 ml.[14] However, the volume of CSF is not a complete explanation for such interindividual variations because it has been shown that onset and offset times of anesthesia are not correlated with CSF volume at the lumbar level.[20]

We concluded that volume did not modify the time course of sensory blockade of either isobaric or hyperbaric bupivacaine. The use of large volumes led to less intense motor blockade with hyperbaric bupivacaine, which may be the result of restricted diffusion of hyperbaric bupivacaine in the CSF. Our results show that a hyperbaric solution induces shorter anesthesia and motor blockade than an isobaric solution. Small doses of hyperbaric bupivacaine may be an alternative to spinal lidocaine for short procedures.

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