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Research Article

Cardiovascular Safety of Isobaric Levobupivacaine versus Hyperbaric Bupivacaine for Spinal Anesthesia in Patients 65 Years or Older Undergoing Hip Surgery

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Abstract

Background: The arterial hypotension is the most frequent adverse effect after subarachnoid anesthesia. The aim of the study was to determine local anesthetic selection's role underlying spinal anesthesia-induced hypotension. We conducted a phase IV randomized single-blind clinical trial to assess the hemodynamic impact of subarachnoid anesthesia with isobaric levobupivacaine (LEVO) versus hyperbaric bupivacaine (BUPI) for hip fracture surgery.

Description: Hundred fifty ASA status I-IV patients aged 65 and older undergoing hip fracture surgery were enrolled. The primary objective was to compare hemodynamic effects based on invasive systolic/diastolic blood pressure (ISBP and IDBP), heart rate (HR), hemoglobin (Hb), diuresis, on respiratory effects, on arterial blood gases and on requirements of vasoconstrictors and liquids. The secondary objective was to assess adverse events preoperatively, 30 minutes after and end of anesthesia and 48 hours after anesthesia. Among intraoperative events, there were no statistically significant differences in the main study variables between groups. There was a reduction in both ISBP as IDBP at 30 minutes (no statistically significant differences). In LEVO, reduced values of HR of 7% at 30 minutes was observed. Only 6 patients of BUPI group received phenylephrine. The mean dose of ephedrine during anesthesia was higher in BUPI ($p<0.01$). More patients in BUPI group received colloids but difference was not statistically significant. Vomiting occurred in BUPI (6%). Among events at 48 hours, transfusion of red blood cells and vomiting were frequent in both groups.

Conclusions: As isobaric levobupivacaine produces less vasoconstrictor requirement and hemodynamic changes, it could be the anesthestic of choice for subarachnoid anesthesia in elderly patients.

Keywords: Elderly; Hip fracture; Subaracnoid block; Levobupivacaine; Bupivacaine

Introduction

It is estimated that in 1990 occurred 1.7 million hip fractures worldwide [1]. The number continues to grow, due to the combination of the increase in the elderly population and increasing longevity. Rockwood [2] even proposes the term epidemic. It is anticipated that by 2050 the global figure will be 6.26 million hip fractures [3] and the European Community will exceed 1 million fractures [4].

Perioperative morbidity and mortality may be influenced by both the anesthetic solution [5] and the surgical procedures. Pathophysiological changes associated with aging, significant comorbidities, treatment with multiple medications and a reduced functional reserve render the elderly more vulnerable to the pharmacological effects of drugs in general and particularly to local and general anesthetics [6]. Racemic bupivacaine is considered the long-acting local anesthetic of choice in several regional anesthetic procedures [7-9], especially for subarachnoid administration. Levobupivacaine is the S-enantiomer of racemic bupivacaine. Clinical studies have shown that bupivacaine and levobupivacaine are equally effective [5,10], however, levobupivacaine has lower affinity for sodium channels in the heart [11], and therefore it is less frequently associated with cardiovascular events. Recent systematic reviews [12] suggest that neuraxial (subarachnoid and epidural) regional techniques could reduce the relative risk of postoperative mortality and the relative risk of deep vein thrombosis, but had not significant impact on other postoperative complications or on the 1-month mortality [13].

There is little evidence comparing the use of levobupivacaine [10] versus bupivacaine, either in clinical practice [14,15] or in studies assessing the safety of one versus the other [16-18]. Assessments were conducted preoperatively, at 30 minutes after anesthesia, at the end of anesthesia (when the patient could be transferred to the post surgical recovery unit), and at 48 hours of anesthesia. The ideal subarachnoid block for management of aged 65 and older undergoing hip surgery remains elusive, especially in respect of dosing and local anesthetic selection. To explore these issues, we compare two differing local anesthetics (LA) formulations.

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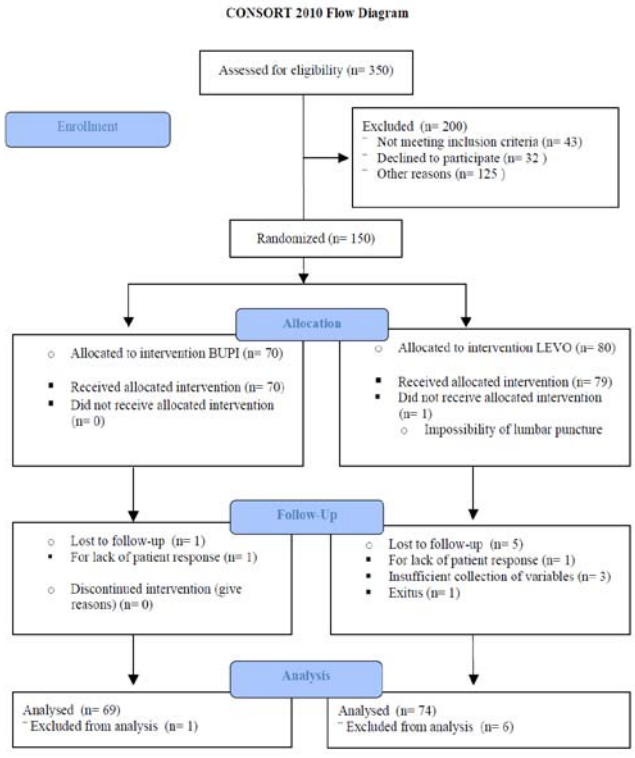

Figure 1: Flowchart of progress through the stages of recruitment, assignment, monitoring and analysis of patients BUPI and LEVO clinical trial (COLEBANES) groups.

The primary objective of our study was to compare the cardiovascular safety of subarachnoid anesthesia with isobaric levobupivacaine versus hyperbaric bupivacaine.

Patients and Methods

This was a phase IV, randomized, single blind clinical trial to assess the hemodynamic effects of subarachnoid anesthesia with isobaric levobupivacaine versus hyperbaric bupivacaine in 150 ASA status I-IV patients aged 65 and older undergoing hip fracture surgery at Consorci Hospital General Universitari (CHGUV), València, Spain. Assessments were conducted preoperatively, at 30 minutes of the anesthesia, at the end of anesthesia and at 48 hours postoperatively. As shown in the flowchart CONSORT 2010, a total of 150 patients were included, 74 patients were analysed in the isobaric levobupivacaine group and 69 in the hyperbaric bupivacaine group (Figure 1). Patients were randomized into two groups based on the type of anesthetic solution used: LEVO group included patients with 0.5% isobaric levobupivacaine (Chirocane™, Abbott) plus fentanyl (solution LEVO), and BUPI group included patients with 0.5% hyperbaric bupivacaine (Braun, Rubí, Spain) plus fentanyl (solution BUPI). The doses used hyperbaric bupivacaine or levobupivacaine were 6 mg in both cases and the fentanyl dose of 10 μg in both cases.

Inclusion criteria were as follows: males and females aged 65 or older diagnosed with a hip fracture and treated with intrathecal anesthesia with levobupivacaine plus fentanyl or bupivacaine plus fentanyl; patients classified as I-IV according to the American Society of Anesthesiologists (ASA); body weight > 40 kg; height > 140 cm; body mass index (BMI) < 50 kg/m^2.

Exclusion criteria were as follows: patients with uncontrolled hypertension (systolic blood pressure values noninvasive > 180 mmHg and / or diastolic blood pressure noninvasive > 110 mmHg; HR> 120 bpm, SpO_2 < 90% on arrival to the operating room; with contraindication for neuraxial anesthesia (infection at the puncture site or different puncture, degenerative neuromuscular disease, hypovolemia, coagulopathy or anticoagulant therapy, extreme morbid obesity and increased intracranial pressure); patient refusal.

Before the clinical trial was initiated, approval was obtained from the Research Commission and the Clinical Research Ethics Committee at the Department of Health of València, Hospital General (EudraCT no. 2012-005559-17) and the project was reviewed by the Spanish Regulatory Drug Agency (AEMPS) which assigned a sponsor protocol code ACA-SPAI-12-07. The study was conducted in accordance with the principles laid out in the Declaration of Helsinki and the applicable law and regulations governing personal data protection and rights and responsibilities regarding information and documentation in healthcare.

The standard subarachnoid technique was applied, to the patient placed in the lateral position with the affected limb raised. After sterilizing the anesthetic field, local infiltration was performed using 2% lidocaine. Both anesthetic solution LEVO and BUPI were administered by the anesthesiologist (from the Anesthesiology department allocated to the operating room (OR) according to the hospital's organizational chart) aseptically in the subarachnoid space using a Whitacre 25 G needle. Puncture was performed using the midline or paramedian approach in intervertebral spaces L2-L3, L3-L4 or L4-L5, with the bevel in the cephalic direction. After confirmation of clear cerebrospinal fluid (CSF) efflux, solution LEVO (n= 70) or solution BUPI (n =80) was administered. The solution was injected with or without prior aspiration of CSF.

Once the subarachnoid puncture was completed, patients were placed in the supine position and urinary catheterization was performed. Patients were moved off the bed onto the surgical table, where they were positioned for surgery in the lateral or supine position according to the fixation material to be implanted.

As a single-blind study the subject was unaware of the treatment group that was assigned randomly while the researcher knew it. A number of 150 patients were included consecutively and data was collected. To ensure personal data protection, the sample was treated anonymously by using a double listing assigning a number with three digits (001, 002, ...) to each patient from 001 to 150.

All data were recorded in a data collection notebook designed for this purpose. A plan for data management was developed including all documentation and management activities data related to the study. It included: validating the database, guidelines for data entry, validation plan and quality checks, collection of data assessment and the statistical analysis plan.

It was intended that all patients would end up the process within safety and informed consent limits. None of the patients removed was included later. When appropriate, investigator could withdraw a patient from the study with a justified reason. He could stop the

Table 1: Characteristics of patients at baseline.
BUPI = hyperbaric bupivacaine; LEVO = isobaric levobupivacaine; BMI= body mass index; Osteosynthesis (OS); Partial Hip Prosthesis (PHP); Total Hip Prosthesis (THP); Arthroplasty (ARP); Dynamic Hip System plates (DHS); GAMMA plates (GAMMA); Condylar Nail-Plates (DCS); Others (Oth).

A. Socio-demographic variables expressed as mean (SD).

		Total (N= 143)	Bupivacaine (N= 69)				Levobupivacaine (N= 74)			
		%	N	%	Mean	SD	N	%	Mean	SD
GENDER	Man	24	15	22.0			19	26.0		
	Woman	76	54	78.0			55	74.0		
AGE (years)					83.0	7.0			84.0	6.3
WEIGHT (kg)					65.0	10.0			67.0	13.0
SIZE (cm)					158.0	8.0			161.0	7.8
BMI (kg/m2)					26.0	4.0			26.0	4.4

B. Clinical Variables.

		Total (N=143)		BUPI (N=69)		LEVO (N=74)	
		N	%	N	%	N	%
Gender	Man		24	15	22.0	19	26.0
	Woman		76	54	78.0	55	74.0
BASIC PATHOLOGY	RESPIRATORY	16	11.0	9	13.0	7	10.0
	VASCULAR	103	72.0	51	74.0	52	70.0
	NEUROLOGICAL	53	37.0	23	33.0	30	41.0
	CARDIAC	47	33.0	22	32.0	25	34.0
	HEPATIC/ RENAL	27	19.0	13	19.0	14	19.0
	ENDOCRINE/ METABOLIC	94	66.0	45	65.0	49	66.0
	HISTORY OF ANTI-PLATELET OR ANTICOAGULANT AGENT	8	6.0	6	9.0	2	3.0
SPINAL LEVEL	L2-L3	11	8.0	4	6.0	7	6.0
	L3-L4	58	41.0	26	38.0	32	43.0
	L4-L5	74	52.0	39	57.0	35	47.0

		BUPI (N=69)	LEVO (N=74)
		%	%
TYPE OF HIP FRACTURE	Subcapital fracture	32.0	23.0
	Transcervical fracture	1.0	1.0
	Basicervical fracture	0.0	8.0
	Pertrochanteric fracture	61.0	49.0
	Subtrochanteric fracture	6.0	19.0
OSTEOSYNTHESIS IMPLANT TYPE	Osteosynthesis (OS)	30.0	43.0
	Partial hip prosthesis (PHP)	23.0	20.0
	Total hip prosthesis (THP)	1.0	1.0
	Dynamic Hip System plates (DHS)	30.0	26.0
	GAMMA plates (GAMMA)	3.0	1.0
	Others (Oth)	13.0	8.0

BUPI = hyperbaric bupivacaine; LEVO = isobaric levobupivacaine; BMI= body mass index.

treatment and the patient could be removed from the study for the following reasons. Own request, without giving reasons; by efficiency criteria: when the patient received the stipulated medication regimen in the test and showed a deterioration in their clinical condition that required to initiate treatment with another medication not permitted in this protocol. Patients that show "Lack of response" during the active treatment phase; by safety criteria: appearance of serious pathology which led to a change in the patient's clinical condition preventing the entire active treatment phase. If there were adverse events (including intercurrent diseases), which prevented the study medication to continue; premature treatment discontinuation: when there was a premature completion of the study, whenever possible,

the patient underwent a final exam, in which the expected procedures were followed.

The following socio-demographic variables were collected: patient data, including unique code number (consecutive study number), gender, age (years), body weight (kg), height (cm), and BMI (kg/m^2); presence of CV, respiratory, neurological, hepatic/renal or endocrine/metabolic disease, history of anti-platelet or anticoagulant agent use prior to surgery; type of hip fracture and hospital stay in days.

Before surgery initiation, anesthesiologists checked sensory and motor blocks. The sensory block level was assessed using the pinprick test (1 = hypoalgesia; 2 = analgesia; 3 = analgesia plus hypoesthesia; and 4 = anesthesia) using a 22 G blunt hypodermal needle. The motor block level was assessed using the modified Bromage scale (0 = no motor block, able to flex hips, knees and ankles; 1 = just able to flex knees, unable to extend legs; 2 = able to move ankles, unable to flex knees; 3 = unable to flex ankles, knees or hips, complete motor block).

Anesthetic and surgical technique variables were collected, such as level of puncture (L2-L3, L3-L4, or L4-L5); type of hip fracture and surgical implant; and surgical and anesthetic times in minutes.

Once the patient was installed on the preoperating room, we proceeded to access an intravenous needle 20 G, 18 G or 16 G as easily puncture and to administrate an intravenous of 1000 ml of crystalloid or colloid in 30 minutes and antibiotic prophylaxis with 2 grams of cefazolin if there was no allergy to beta-lactams, in which case clindamycin 600 mg was administrated by intravenous access. Patient received premedication with 1 milligram of midazolam associated 25 micrograms of both intravenous fentanyl. Then the patient was moved to the operating room where we proceeded with the patient in supine position, to hemodynamic monitoring.

Non invasive hemodynamic monitoring occurred by placing six electrocardiographic leads, heart rate (HR) measured in beats per minute (bpm), the oxygen saturation in % expressed through a pulse oximeter placed on the index finger (SpO_2%) and diuresis.

Invasive hemodynamic monitoring blood pressures systolic and diastolic (ISBP and IDBP) measured in mmHg and arterial blood gases (hemoglobin in g/dL, PaO_2 in mmHg, SaO_2 in mmHg and $PaCO_2$ in mmHg, pH and lactate in mmol/L)

Requirements of vasoconstrictors (ephedrine and / or phenylephrine, and / or atropine) and liquids (crystalloid and / or colloids) were recorded.

Information was collected on potential adverse events during the intraoperative period. Hypotension and bradycardia were defined as a reduction from baseline by > 20% in mean arterial pressure (MAP) and HR, respectively. Adverse events included CV and respiratory events, such as venous gas embolism, deep vein thrombosis (DVT), acute myocardial infarction (AMI), stroke, congestive heart failure (CHF), pneumonia or death, and other events such as acute renal failure (ARF) and vomiting. Surgical procedure associated events included red blood cells transfusion (RBC), plasma transfusion (PT), nerve injury (NI), femur fracture; (FF) events associated with the anesthetic procedure included paresthesia, bloody puncture, and others.

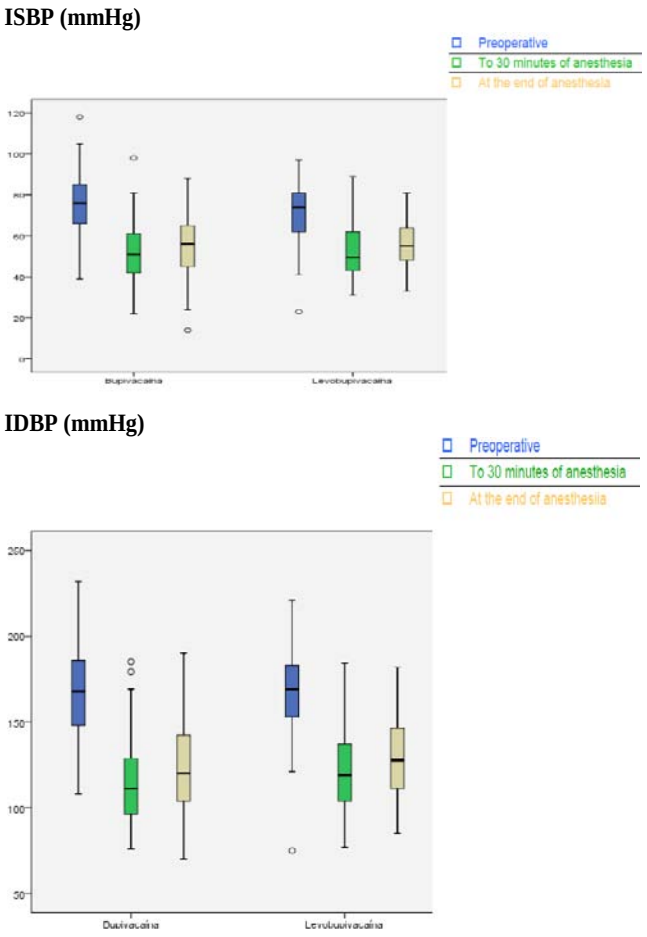

Figure 2: Variation in values of ISBP and IDBP, registered to the entry into the operating room, at 30 minutes of anesthesia and end of anesthesia. ISBP = invasive systolic blood pressure; IDBP = invasive diastolic blood pressure; bupivacaína = bupivacaine and levobupivacaína = levobupivacaine; 0 = atypical value.

The assessment performed at 48 hours postoperatively included the following adverse events: DVT, AMI, stroke, CHF, pneumonia and death; and others such as ARF, urinary tract infection, and vomiting. Surgical procedure associated events included RBC transfusion (anesthesiologist's choice), plasma transfusion, neurological deficits and surgical site infection.

With a sample size of 150 patients (74 in LEVO and 69 in BUPI groups), the study had 85% statistical power to detect minimal differences between groups of 20 mmHg in ISBP and IDBP, 20 bpm in HR, 5 g Hb, and 2 percentage points in partial oxygen saturation. A specific case report form was developed for this study and the data were transferred to the SPSS 15.0 software for Windows. The information in the database was checked for quality to avoid inconsistencies and duplicated or inaccurate data. Descriptive statistics were used and the arithmetic mean and the standard deviation were determined for each variable. Comparisons between groups were performed using the Friedman test. The Mann-Whitney test was used to assess the groups for homogeneity. Pearson's chi-squared test and Fisher's exact test were used to assess associations between qualitative variables. Significance was set at $p < 0.05$. The study was conducted without

Table 2: Effect of bupivacaine and of levobupivacaine on invasive systolic blood pressure (ISBP) and invasive diastolic blood pressure (IDBP) to the entry in OR admission, at 30 minutes of anesthesia and end of anesthesia. No significant difference in ISBP change at 30 minutes after anesthesia onset (p >0.05).

ISBP (mmHg)		Total (N= 143)	BUPI (N=69)	LEVO (N=74)
PREOPERATIVE	Mean	168.0	168.0	167.0
	SD	25.0	26.0	24.4
TO 30 MINUTES OF ANESTHESIA	Mean	119.0	115.4	123.0
	SD	25.8	26.0	25.0
AT THE END OF ANESTHESIA	Mean	127.0	125.0	129.0
	SD	26.3	28.0	24.7
IDBP (mmHg)				
PREOPERATIVE	Mean	73.0	75.0	72.0
	SD	15.0	15.0	15.0
TO 30 MINUTES OF ANESTHESIA	Mean	53.0	52.0	53.0
	SD	13.0	13.0	12.0
AT THE END OF ANESTHESIA	Mean	56.0	56.0	56.0
	SD	13.0	14.0	12.0

SD= standard deviation.

funding from Abbott Laboratories.

Results

Both patient groups had similar socio-demographic characteristics and comorbidities. The mean age was 80 years; 76% were women (Table 1A). All underwent surgery for hip fracture with no significant differences between the two groups regarding the type of fracture, or the type of implant (Table 1B). Anesthesia was performed as planned in the protocol in all patients included in the analysis. For one patient in LEVO group it was not possible lumbar puncture so the case was excluded from the study and therefore was not included in the analysis of the data. Table IB shows the levels of lumbar puncture, the most frequent was L4-L5 in both groups. In all cases the variables were recorded envisaged in the protocol.

Upon entry into the operating room mean invasive systolic blood pressure (ISBP) was 168.0 ± 25.0 mmHg and mean invasive diastolic blood pressure (IDBP) was 73.0 ± 15.3 mmHg. At the end of anesthesia none of the values showed statistically significant differences from the initial (mean ISBP 127.0 ± 26.0 mmHg and mean IDBP 56.0 ± 13.0 mmHg) (Table 2). In both groups a reduction ISBP and IDBP values from 30 minutes of anesthesia was observed. In the BUPI group (mean ISBP 115.36 ± 26.32 mmHg and mean IDBP 53.0 ± 13.0 mmHg), the downward trend was higher than in the LEVO group (mean ISBP 123.0 ± 25.0 mmHg and mean IDBP 53.0 ± 12.0 mmHg). That trend continued until the end of anesthesia but there were no statistically significant differences (Figure 2).

The initial values of heart rate (HR) were similar in both groups. In the LEVO group a reduction of 7% at 30 minutes of anesthesia was observed (entry into the operating room, 85 bpm with BUPI, 86 bpm with LEVO, to 30 minutes of anesthesia, 86 bpm with BUPI and 81 bpm with LEVO), maintaining the trend until the end of the anesthesia (Figure 3).

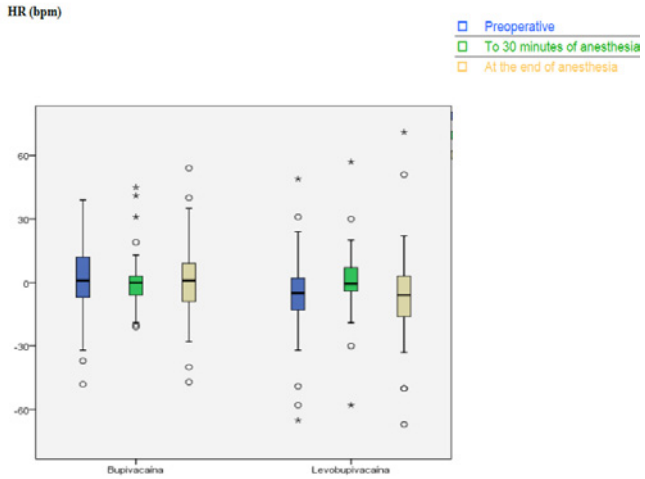

Figure 3: Heart rate (HR) values according to anesthesia time point; bupivacaína = bupivacaine and levobupivacaína = levobupivacaine; HR (bpm) = heart rate measured in beats per minute; 0 = atypical value; ★ = extreme value; ★ = p <0.01.

Table 3: Number of patients requiring phenylephrine (mcg) along anesthesia in both groups; mcg= micrograms.

Phenylephrine (mcg)	BUPI (N=69)		LEVO (N=74)	
	Total	%	Total	%
PREOPERATIVE	2.0	3.0	0.0	0.0
TO 30 MINUTES OF ANESTHESIA	3.0	4.0	0.0	0.0
AT THE END OF ANESTHESIA	3.0	4.0	0.0	0.0

No statistically significant differences between groups were found in the following main variables of the study (SpO_2 (%), PaO_2 (mmHg), $PaCO_2$ (mmHg), SaO_2 (mmHg), Hb (g/dl), pH, Lactate (mmol/L), diuresis (ml)).

The use of vasoconstrictor drugs was performed according to the needs of the patient as indicated in the protocol. They were administered immediately after subarachnoid block when there was an invasive reduction of baseline over 20% or an invasive blood pressure. Phenylephrine received only by some patients from BUPI group (Table 3), while both patients groups required ephedrine along anesthesia. The use of ephedrine was significantly higher in the BUPI group as 41 patients immediately after subarachnoid block, 28 to 30 minutes and 10 at the end versus 4, 10 and 2 patients respectively LEVO group (Figure 4 and 5). The mean dose of ephedrine was higher in the BUPI group, the first administration was 17 times the LEVO group, with minor differences within 30 minutes and at the end of anesthesia (Table 4). The proportion of patients who needed ephedrine during anesthesia was higher in the BUPI group (p <0.01). After 30 minutes of anesthesia the proportion of patients who received

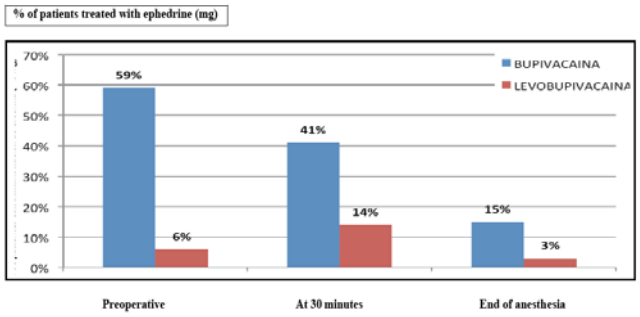

Figure 4: Proportion of patients in the BUPI and LEVO groups receiving ephedrine within 3 times of the study; bupivacaína = bupivacaine and levobupivacaína = levobupivacaine.

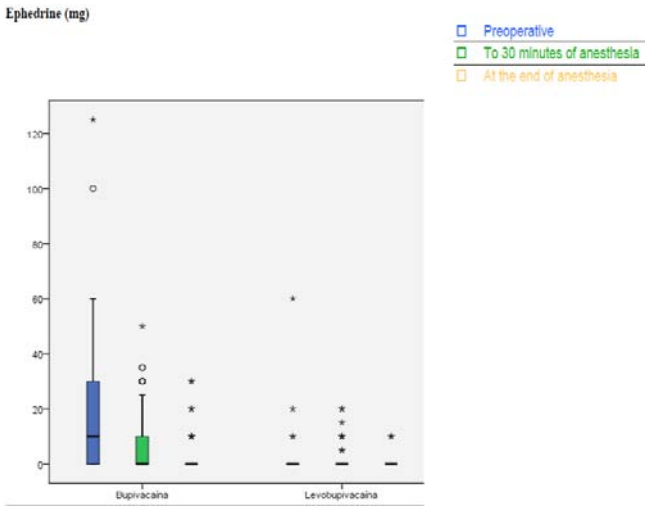

Figure 5: Requirements for ephedrine after entry, at 30 minutes and at the end of anesthesia in the BUPI and LEVO groups; ephedrine (mg) in milligrams; 0 = atypical value; ★ = extreme value.

Table 4: Ephedrine dose (mg) administered 3 times anesthetics in BUPI and LEVO groups (p <0.01).

Ephedrine (mg)		Total (N= 143)	BUPI (N=69)	LEVO (N=74)
PREOPERATIVE	Mean	9.0	17.0★	1.0
	SD	19.0	23.0	8.0
TO 30 MINUTES OF ANESTHESIA	Mean	5.0	8.0★	2.0
	SD	9.0	12.0	4.0
AT THE END OF ANESTHESIA	Mean	1.0	2.0	0.0
	SD	5.0	7.0	2.0

Ephedrine (mg) in milligrams; ★ =p<0.01; SD= standard deviation.

ephedrine was lower in both groups, but the percentages were always higher in the BUPI group (41% in BUPI and 15% in LEVO) to the end of anesthesia (14% in BUPI and 3% by LEVO) (Figures 4 and 5).

According to the protocol, after entering the operating room, all patients received 1000 ml of crystalloid (Table 5); then it was administered as needed. After 30 minutes of anesthesia it was necessary to administer about 350 ml and at the end of anesthesia a lower volume (Figure 6). There were no significant differences between the two groups. More patients in BUPI group received colloids during the three anesthetic times (9, 39 and 48 in the BUPI group and 5, 27 and 30 in LEVO group) as shown in Figure 6. There were no statistically significant differences between the volumes of colloids used in the two groups.

Table 5: Crystalloid volume administered since the entry into the operating room until the end of anesthesia.

Crystalloid volume administered (ml)		Total (N= 143)	BUPI (N=69)	LEVO (N=74)
PREOPERATIVE	Mean	1140.0	1157.0	1125.0
	SD	202.0	255.0	138.0
TO 30 MINUTES OF ANESTHESIA	Mean	346.0	359.0	333.0
	SD	236.0	237.0	236.0
AT THE END OF ANESTHESIA	Mean	198.0	173.0	222.0
	SD	165.0	156.0	170.0

SD= standard deviation.

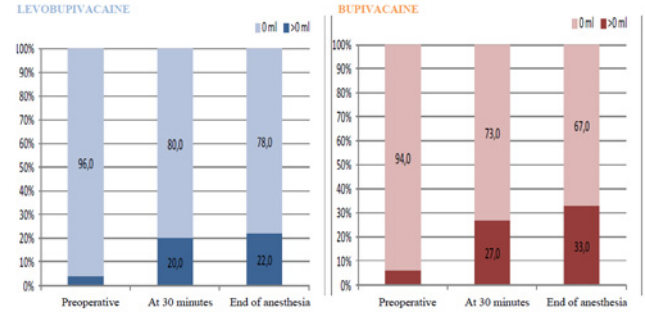

Figure 6: Percentage of patients receiving colloids over 3 times the study.

Table 6: Percentage of the most frequent intraoperative events in the groups treated with bupivacaine and levobupivacaine.

More frequent intraoperative events	BUPI (N=69)	LEVO (N=74)
	%	%
Congestive heart failure	1.0	0.0
Vomiting	6.0	0.0
RBC transfusion	46.0	42.0
Plasma transfusion	1.0	0.0
Femur fracture	0.0	1.0
Other rare	0.0	1.0

RBC transfusion= red blood cells transfusion.

Table 7: Percentage of the most frequent postoperative events produced at 48 hours of anesthesia in the groups treated with bupivacaine and levobupivacaine.

More frequent postoperative events	BUPI (N=69)	LEVO (N=74)
	%	%
DVT	1.0	0.0
Stroke	0.0	1.0
Exitus	1.0	0.0
Acute renal failure	3.0	0.0
Vomiting	3.0	3.0
RBC transfusion	9.0	11.0

DVT= deep venous thrombosis; RBC transfusion= red blood cells transfusio.

Intraoperative events are shown in Table 6. The most frequent were RBC transfusion associated with the surgical technique in both

groups, followed by vomiting that only occurred in the BUPI group. The most common postoperative events collected at 48 hours of anesthesia were RBC transfusion and vomiting in both groups (Table 7). In the BUPI group there was one case of deep vein thrombosis, two of acute renal failure and one death. In the LEVO group was one case of stroke.

The mean time of anesthesia was 90 minutes and the mean time of surgery was 65 minutes. The mean hospital stay was about 9 days; the mean value in BUPI group was 9.1 days (maximum of 64 days, minimum of 5 days), and in the LEVO group 8.4 days (maximum 19 days, minimum 5 days).

Discussion

Our interest in developing this study was to observe hemodynamic safety after subarachnoid administration of an isobaric or hyperbaric anesthetic and with the obtained results, to contribute to improve both postoperative outcomes and clinical practice of patients undergoing hip fracture surgery. In 2012 we decided to conduct a post-marketing, retrospective follow up study [19] to assess the hemodynamic impact of levobupivacaine and hyperbaric bupivacaine in patients with 65 or more years with hip fracture and to ensure the safety of these two molecules with different baricity in this patient profile. The conclusions encouraged us to initiate this clinical trial. Later we'll comment both studies results and among others.

Although it was not the aim of this study to compare efficiency of anesthetic treatments, these were sufficiently effective and allowed the development of surgery in all patients included in the analysis of results. All variables that were analyzed changed similarly in both groups throughout anesthesia, with the exception of the heart rate decreased slightly from 30 minutes in the LEVO group. This result agreed with those obtained by Glaser [20] and Fattorini [21], comparing isobaric levobupivacaine 0.5% (15 mg) in 20 patients with bupivacaine 0.5% (15 mg) in 60 patients, undergoing lower limbs surgery. There was no significant reduction in heart rate in either group. However, Alonso Chico [22] detected a significant increase in the values of HR with hyperbaric bupivacaine (N=30) which concurred with episodes of hypotension and simultaneous administration of ephedrine, to 30 minutes of anesthesia and it related to the hyperbaricity. Changes in HR seem therefore due to the baricity of the solution used, but in our study we observed no changes in the group that received the hyperbaric solution.

During anesthesia, the blood pressure values decreased in both groups. The usual treatment of perioperative hypotension is to place the patient in Trendelenburg position if feasible, to administer vasopressors and to infuse crystalloid and / or colloid. Vasopressor drugs most used in intraoperative anesthetic practice are ephedrine and phenylephrine, both have a suitable pharmacological profile for treating patients with different diseases, especially cardiovascular, respiratory and endocrine type. The use of alpha-adrenergic stimulants such as phenylephrine raises blood pressure but can reduce cardiac output by concomitant increased after load. Moreover, mixed adrenergic agonists, alpha and beta, as ephedrine, increase heart rate and cardiac output with slight effect on systemic vascular resistance [23].

Our results show statistically significant differences in the requirements of vasoconstrictor drugs, motivated by the appearance of hypotension after the subarachnoid administration of LA. Most of the patients who presented hypotension received ephedrine, while some of BUPI group received phenylephrine. The use of ephedrine is preferred because it increases blood pressure, heart rate, cardiac output and bronchodilator. The use of phenylephrine is restricted to those patients in whom increased heart rate secondary to the use of ephedrine may be inadvisable, as in case of a trial fibrillation or taquicardia [24]. In our study, the use of ephedrine was much higher in the BUPI group, whether we look at the number of patients who received at each of the anesthetic times as the dose used, indicating that patients receiving hyperbaric bupivacaine presented hypotension more frequent and of greater magnitude than those who received isobaric levobupivacaine.

In our study, both groups of patients were homogeneous, received the same preoperative treatment, the same dose of local anesthetic, 6 mg, and were maintained in the same lateral decubitus position with the prone position fractured limb. Therefore, differences that can be observed are attributable to baricity of the anesthetic solution.

The study of Fernández Vázquez [25] with 256 patients compared sympathetic blockade following administration of isobaric bupivacaine (group I) and hyperbaric bupivacaine (group H). He detected those 24 patients in group H and 4 in group I require ephedrine in the first 30 minutes of anesthesia, with a significant difference between groups. These results concurred with those of Alonso Chico [22], who administered ephedrine for hypotension in 28 of the 60 patients treated with hyperbaric bupivacaine, total dose was greater in the group that received fentanyl (190 mg group B vs 40 mg group BF). Errando [26] also used hyperbaric bupivacaine (0.5% vs 0.375%) for hip fracture surgery and found that 27 of the 61 patients required ephedrine. Glaser [20] in the study (80 patients), administered phenylephrine after anesthesia in only 1 patient isobaric levobupivacaine group and only in 2 patients in group isobaric bupivacaine 0.5%.

In a prospective observational study by Carpenter [27] in almost 1000 patients, the incidence of hypotension was high (33%) and this concurred with the results of the Cochrane review [13]. Other authors describe a low prevalence of intraoperative hypotension with the use of isobaric anesthetic to repair a hip fracture. The exact mechanism is uncertain, but may be injecting isobaric anesthetics into the subarachnoid has the effect of limiting the height of sympathetic blockade below T6 [28] and produces less hypotensive effect. Carpenter [27] studied 952 patients treated with hyperbaric, hypobaric and isobaric solutions, predominantly treated with hyperbaric (90%) solution. It found hypotension in 314 (33%) of all patients without specifying the type of solution, but if 90% received hyperbaric anesthetic, hypotension should occur mainly in this group. The results of our previous retrospective study [19] showed that 38% of patients treated with hyperbaric bupivacaine presented hypotension after 30 minutes of anesthesia. These results concur with those of Errando [26] where double-blind randomized patients treated with hyperbaric bupivacaine presented hypotension at 5, 10 and 15 minutes of anesthesia. Wood [29] also observed hypotension in 94% of patients treated with > 7.5 mg of hyperbaric bupivacaine (N= 463) on a total of 578 patients undergoing hip fracture. Our

results with those reported by other authors suggest that hyperbaric formulations induce hypotension more often and greater magnitude than the isobaric.

The study of Fattorini [21] compares isobaric levobupivacaine and bupivacaine 0.5% and notes that only 2 patients in the bupivacaine group presented hypotension after spinal block. Similar results obtained Glaser [20] describing hypotension in 2 patients treated with bupivacaine and in one treated with levobupivacaine, both isobaric. In the retrospective study [19] it was observed by our group that the incidence of intraoperative hypotension was significantly lower in the 60 patients treated with isobaric levobupivacaine (13% vs 38% hyperbaric bupivacaine). Ben-David [30] studied two groups of 10 patients older than 70 years who administered 4 and 10 mg of isobaric bupivacaine respectively; they recorded more cases of hypotension in the highest dose group (9/10 patients). Other authors provide a high incidence of intraoperative hypotension with the use of hyperbaric anesthetics [30]. Valued these results together suggest that bupivacaine, regardless of the type of solution used, can cause hypotension. However existing data support the influence of baricity more conclusively than explaining differences between molecules.

If we analyze the fluid requirements during anesthesia, which are related to patient hemodynamic conditions, we note that there are no differences between the two groups regarding the use of crystalloid. However, patients treated with hyperbaric bupivacaine received greater volume of colloids than those treated with isobaric levobupivacaine and volume tended to be higher in the group BUPI from the 30 minutes of anesthesia. This observation also supports an increased frequency of hemodynamic instability in BUPI group, it is difficult to compare these results with those of other authors. In most published studies on hip surgery, is named the type and volume of fluids administered preoperatively in the section "Patients and Methods", but no data given during anesthetic management. Studies about the type and volume of fluids during and at the end of anesthesia are rare. Wood [29] in it retrospective study with 578 patients, described a greater volume of fluid in the group treated with the highest dose of hyperbaric bupivacaine but does not provide the type or volume required during anesthesia group. These results do not match those obtained by Ben-David [30], in which the fluid requirements were similar in patients anesthetized with isobaric bupivacaine different doses (4 mg vs 10 mg). Intravenous rehydration may reduce the incidence of hypotension but not prevented, regardless of the volume infused or use of colloids and / or crystalloids.

The secondary objective of the study was to evaluate the events during anesthesia and 48 hours after. The most frequent event in both groups was the red blood cell transfusion related to surgical technique. These results agree with those obtained by the Cochrane review in 2011 [31], where 6 clinical trials with 2722 participants with data for the number of transfused patients or the mean volume of blood transfused were included. Rodgers [32] reviewed a total of 141 clinical trials involving 9559 patients undergoing spinal anesthesia. It detected 573 cases of transfusion: 473 patients from 16 trials required transfusion of two or more units of blood and 100 patients from 12 trials had postoperative bleeding requiring transfusion of red blood cells.

It is noteworthy that only in the BUPI group vomiting occurs during the surgical time, while in the postoperative period in both groups appears with similar frequency. These results concur with those of Carpenter [27] who described vomiting in 7% of patients who presented hypotension followed with bradycardia and nausea, in a study that 90% of patients received hyperbaric bupivacaine. Bigler [33] and McLaren [34] noted that vomiting occurred frequently after subarachnoid technique concurring with the peak of sympathetic blockade.

In our study, postanesthesia events are rare in both groups and less frequent than those described in the prospective observational study of Roche [35] with 2448 patients undergoing surgery for hip fracture, in which the complication rate was 14% in patients without comorbidity when entering the hospital and 20% had a single postoperative complication. The only case of acute renal failure appeared in the BUPI group. Predisposing factors may trigger, such as the elderly (87 years), the hypertension, the degenerative brain disease and the hypotension during surgery that may reduce renal blood flow. This result agrees with 4 studies [34,36-38] including hip fractures treated with spinal anesthesia but not defining the local anesthetic type. The only case of DVT and exit us appeared in the BUPI group, which could be related to the patient's age (86 years), with a history of hypertension and dyslipidemia and the increased incidence of DVT associated with the emergency surgery. The incidence is low if we consider the risk of DVT inherent in this type of surgery and elderly patients. In the 141 clinical trials reviewed by Rodgers [32] with 9559 patients undergoing spinal anesthesia, they were described a total of 365 cases of DVT. The case of stroke appeared in the LEVO group, in a patient 78 years old, with predisposing factors such as chronic bronchitis, hypertension, type II DM and dyslipidemia, which along with the type of surgery, brought on the occurrence of this event. Several studies included in the Cochrane review [13] relates the occurrence of stroke in these patients with perioperative hypotension.

The study had limitations, anesthtetic dynamics and type of instrumentation used made impossible to record the values of the main variables continuously. Another limitation was that we included patients 65 years or older but not age ranges. The results could differ if the inclusion had been performed with elderly patients, due to the difference of comorbidities inherent to this age, although the mean age in our study was 80 years. We also arose the question whether preoperative hydration with 1000 ml of crystalloid is excessive in the study population and impacting adversely on hemodynamics of heart disease, respiratory disease, etc. We will consider those observations for our future studies.

Conclusions

We conclude from our study that subarachnoid administration of 0.5% isobaric levobupivacaine plus fentanyl in elderly patients undergoing hip fracture surgery was safer and as effective as the administration of hyperbaric bupivacaine plus fentanyl. Perioperative adverse events 48 hours after surgery are slightly more frequent and more severe with hyperbaric bupivacaine than with isobaric levobupivacaine and suggest that subarachnoid isobaric levobupivacaine should be used instead of hyperbaric bupivacaine in elderly patients undergoing surgical hip fracture repair.

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