

The anaesthetic and recovery profile of two concentrations (0.25% and 0.50%), of intrathecal isobaric Levobupivacaine for combined spinal-epidural (CSE) anaesthesia in patients undergoing modified Stark method caesarean delivery: a double blinded randomized trial

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Abstract. – BACKGROUND: In spinal anaesthesia for a Caesarean delivery, it is important to limit anaesthesia only at the surgical area, and to resolve fast motor block. We compared the intraoperative effectiveness, hemodynamic effects, anaesthetic recovery times and patients satisfaction after isobaric levobupivacaine (L) 0.25% versus L0.50% spinal anaesthesia during elective Caesarean deliveries performed with the Stark technique.

PATIENTS AND METHODS: In this double-blinded prospective study, seventy women undergoing elective caesarean delivery were randomized to receive either intrathecal 7.5 mg Levobupivacaine 0.25% plus sufentanil 2.5 µg (Group L_{0.25}), or intrathecal 7.5 mg L 0.50% plus sufentanil 2.5 µg (Group_{Control}). The onset time, duration of anaesthesia, analgesia and sensory and motor block and hemodynamic parameters were measured from the beginning of spinal anaesthesia until four hours after spinal anaesthesia (T₂₄₀).

RESULTS: Onset time, duration of anaesthesia and haemodynamic variations were similar in the two groups. No patients required general anaesthesia to complete surgery. Motor block vanished faster in Group L_{0.25} as compared with Group_{Control} ($p < .01$). The cephalad spread of the 0.50% solution was higher than that of the 0.25% solution: no patient in Group L_{0.25} experienced paresthesia of the upper limbs vs 14% in Group_{Control} ($p < .05$). In Group_{Control} anaesthesia reached the dermatome T1 in 15% of cases. Maternal and surgeon satisfaction was good in every patient.

CONCLUSIONS: Levobupivacaine 7.5 milligrams at 0.25% may be used as a suitable alternative to L 0.50% for spinal anaesthesia for caesarean deliveries with the Stark technique with good maternal satisfaction. In Group L0.25 a lower appearance of nausea and hypotension were observed and motor and sensitive block developed and diminished faster while no clinically significant differences in hemodynamic behavior was observed between groups.

Key Words:

Levobupivacaine, Combined spinal-epidural anaesthesia (CSE), Caesarean delivery, Stark technique.

Introduction

Caesarean delivery are among those surgical procedures that require a very strict teamwork between surgeons and anaesthesiologists, since the primary goal is to enable a rapid delivery, without foetal and/or maternal side effects. The Misgav Ladach method, or modified Stark method¹, is by far the most utilized surgical technique to perform caesarean delivery, because it is rapid, requires a short time of uterus exteriorization and allows a quick postoperative recovery with less febrile reactions and peritoneal adhesions and fast return to normal bowel function, thus reducing either short and long-term maternal morbidity^{1,2}, whereas neuraxial anaesthesia is the gold standard anaesthesia technique³.

Several studies⁴⁻¹⁰ have been designed in order to find the best dosage of intrathecal local anaesthetic, to obtain the best balance between the need for a good quality analgesia and the need to reduce drug dosages to avoid foetal and maternal side effects. Actually, the use of low concentration of levobupivacaine^{11,12}, with opioid has been demonstrated to achieve adequate analgesia without block's rostral spread and/or excessive side effects such as motor blockade, maternal hemodynamic impairment and subsequent decreased utero placental blood flow^{6,7,9,13}.

This randomized, double-blind, prospective trial was thus launched to test the hypothesis that during combined spinal-epidural (CSE) anaesthesia for elective Caesarean delivery, the subarachnoid administration of constant dose (7.5 mg) isobaric Levobupivacaine would yield a satisfactory spinal anaesthesia in terms of onset and intraoperative analgesia, and would allow shorter recovery times at a concentration of 0.25% and a volume of 3 ml than achieved with 0.5% and a volume of 1.5 ml. Our secondary aim was to compare the haemodynamic effects of such levobupivacaine concentrations.

Patients and Methods

The study was performed in the Obstetrics and Gynaecology Department, University Hospital of Foggia, between May 2011 and January 2013. After local Ethical Committee approval and written informed consent, 90 pregnant women receiving spinal anesthesia for elective cesarean delivery performed by the Stark method^{1,2,10}, were included in the study. Inclusion criteria were: cesarean delivery scheduled for malpresentation, post-term pregnancy in advanced maternal age and macrosomia. We excluded parturients who underwent previous abdominal or gynecological surgery, were in labor, those in whom tubal ligation was planned in the same setting, those with allergy to the study drugs, contraindications to central neuraxial blockade, and obstetric complications, such as infections, preeclampsia, multiple gestation or placenta previa and other placental pathologies. Parturients who were at the extremes of height and weight (body mass index ≥ 20 or ≤ 35 kg/m², height ≥ 145 cm or ≤ 180 cm) were also excluded.

Before the administration of neuraxial anesthesia, an 18-Gauge intravenous cannula was inserted and standard monitors were applied to

each patient. Baseline arterial blood pressure (BP) and heart rate measurements were recorded before the procedure and at 2.5-min intervals throughout the period of study from a noninvasive BP cuff on the right brachial artery with the patients lying supine with a 15° left lateral tilt.

Continuous Spinal Epidural Anaesthesia

Using a computer-generated sequence of numbers, patients were randomly allocated in one of the following groups: Group_{control} (Levobupivacaine 0.50% 1.5 ml + sufentanil 2.5 mcg: total volume 1.5 ml); Group L_{0,25} (Levobupivacaine 0.25% 3 ml + sufentanil 2.5 mcg: total volume 3 ml).

A standardized intra venous "co-load" of 500 ml of a plasma expander and 5 mg intra venous ephedrine was performed coinciding with the sympathetic blockade to all patients.

After local infiltration with 2% mepivacaine, continuous spinal-epidural anaesthesia (CSE) was performed with the patients in the sitting position. The epidural space was identified at L2-3 intervertebral level with an 18-Gauge Tuohy needle using loss of resistance-to-saline technique. A 20-Gauge epidural catheter was positioned 3 cm into epidural space and secured in place for post-operative analgesia. No test dose was performed. Subsequently, a 25-Gauge Whitacre spinal needle (Beckton Dickinson) was advanced at L3-4 intervertebral level through an introducer until cerebrospinal fluid was obtained. The intrathecal dose was injected over 100-120 s and the spinal needle was withdrawn and the patients immediately laid in the supine position with a 10° left lateral tilt.

The physician taking care of the patient was blinded to the group assigned. A blinded independent observer recorded the evolution of sensory and motor blocks on both sides every 5 minutes until readiness to surgery. Assessment of block height was performed on both sides using touch, pinprick and cold in a standardised manner on each patient, using a standardised explanation to patients after the induction of spinal anesthesia, in an ascending fashion starting from the T12 dermatome¹⁴, and assessed by means of the simplified Hollmen³ a binomial scale assessing the presence (score 0) or absence of sensibility (score 1). Motor block was assessed using a modified Bromage score (0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked; 3 = hip, knee and ankle blocked¹⁵).

Loss-of-cold sensation at and including the T6 dermatomal level and a Bromage score of 3 or 4 were considered adequate for surgery. If the block failed to reach this level 15 min after intrathecal injection, epidural anaesthesia was administered and the parturient excluded from the study. After readiness to surgery was achieved, the evolution of sensory and motor blocks was evaluated every 15 minutes until two-segment regression of the sensory level (8,9). Patients were asked to report any intraoperative pain or discomfort using a visual analog scale (VAS) of 0-100 mm. In the event that the VAS was reported as 40 mm or more, or when the sensory block level had receded to dermatome T6, adjuvant systemic analgesics (intravenous fentanyl) or sedative drugs (midazolam) were administered¹⁷.

Perioperative side effects, such as hypotension, bradycardia, nausea and vomiting were also recorded and treated using ephedrine, atropine and ondasetron according with standard protocols. Hypotension was defined as a mean blood pressure (BP) \leq 20% of basal value and treated with additional doses of ephedrine 2.5 mg every 5 minutes until BP returned to the base level. Bradycardia was defined as HR \leq 50 beats/min and was treated with ephedrine or (only with normal blood pressure) atropine 0.2-0.3 mg ev. Neonatal condition was assessed using Apgar scores at 1 and 5 min^{18,19}.

Misgav-Ladach Caesarean Delivery

The modified Misgav-Ladach method for caesarean delivery was used in all cases, with the classical Joel-Cohen laparotomy (JC-L), and the Munro-Kerr low uterine segment incision, as already described^{1-3,16,22}. Briefly, with this technique the uterine incision is performed with no bladder-flap formation, the placental delivery is spontaneous and manual removal never performed. Uterine exteriorization is limited at 10 minutes or less (the time of uterine continuous single suture in single layer and subsequent haemostasis with single stiches), the visceral peritoneum is not sutured, while the parietal peritoneum is closed with a continuous suture. Muscles are not sutured, the fascia is sutured in single continuous Vicryl layer, the subcutaneous tissue with three singles stiches and the skin with an intradermal suture.

Study Steps

BP, HR, SpO₂, VAS were evaluated at T₀ (baseline), T₅ (5 min after spinal block), T₁₀ (10

min after spinal block), T₁₅ (15 minutes after spinal block), T₂₀ (20 min after spinal block), T₃₀ (30 minutes after spinal block), T₄₀ (40 minutes after spinal block), T₁₂₀ and T₂₄₀ (2 and 4 hours after spinal block).

At T₂₄₀, patients satisfaction was also assessed using a descriptive 3-point verbal rating scale (3 extremely satisfied; 2 satisfied; 1 not satisfied). Surgeons were also asked to assess their satisfaction level with the quality of intraoperative conditions according to the same 3-point scale.

Statistical Analysis

A sample size calculation indicated that 28 patients per treatment group should provide a 99% confidence level (assuming $\alpha = .01$) to detect a 30 minutes difference (SD) in motor block duration¹². This number was increased to 35 per group to allow for a 25% patients drop-out rate. Data analysis was performed by means of one-way ANOVA (drug dosage to reverse side effects), and two-ways ANOVA (normally distributed continuous data such as BP, HR and SpO₂). Post-hoc assessment was performed by Fisher's text. The Mann-Whitney rank sum test was used to analyze non-Gaussian distribution of continuous data and ordinal data. Nominal data were analyzed using the χ^2 test. Continuous data are expressed as mean \pm SD. Non continuous data are expressed as number or percentages. A *p* value $<$ 0.05 was considered statistically significant. Statistical analysis was performed using Statistica 8.0 (StatSoft Italia srl, PD, Italy, 2010).

Results

Thirty-five patients in each group received the allocated intervention (see Figure 1).

The two groups were comparable with respect to demographic characteristics, basal hemodynamics parameters, duration of surgery, and local anaesthetic dosage (see Table I).

Adequate levels of sensory analgesia were reached in every patients before surgery (Figure 2). No patient needed epidural anaesthesia supplementation.

The cephalad spread of the 0.50% solution was higher than 0.25% solution: no patients in Group L_{0,25} experienced a cephalad spread $>$ dermatome T5 while paresthesia of the upper limbs was present in 5 patients (14%) in Group_{control} (*p* $<$.05), in which anaesthesia reached the dermatome T1 after ten minutes²¹⁻²⁴.

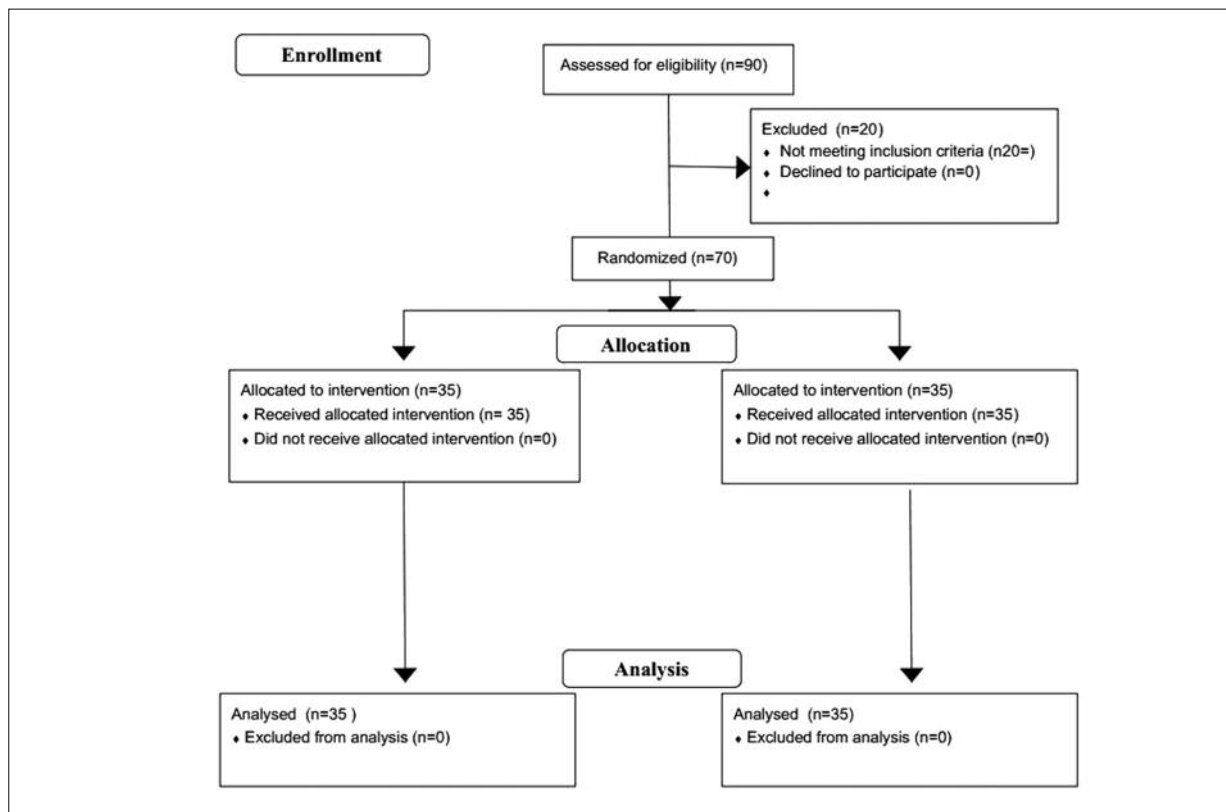


Figure 1. Flow-chart of patients' enrolment throughout the study.

A significant difference in sensitive and motor block resolution was observed between the two groups (Figures 2, 3). After 2 h (T_{120}), no patient in Group $L_{0.25}$ showed residual sensory or motor block, while in Group $control$ both blocks were still present in every patient ($p < 0.05$), and were resolved on T_{240} in all patients²⁴.

Mean BP decreased in every patient after the spinal anaesthesia ($p < 0.05$ T_{10} vs T_0 in all

groups), though it did never reach clinically significant values (Figure 4), and remained stable till the end of surgery (t_{40}). In Group $L_{0.25}$, BP returned to basal values on T_{120} , while in Group $control$ it remained similar to intraoperative values until T_{240} .

Hypotension was observed in 5 patients (14%) in Group $control$, vs none in Group $L_{0.25}$ ($p < .05$). These side effects occurred immediately after spinal puncture. Bradycardia was present in 6

Table I. Patients demographic characteristics.

	Group $L_{0.25}$	Group $L_{0.50}$	Mann-Whitney (χ^2 test)
Age (y)	31.7 ± 5.1	29.8 ± 4.8	N.S.
Weight (kg)	78.8 ± 12.7	75.7 ± 11.3	N.S.
Height (cm)	164.3 ± 5.4	162.8 ± 6.7	N.S.
Duration of surgery (min)	49.2 ± 7.2	49.3 ± 7.4	N.S.
Hypotension N (%)	0°	5 (14%)	$p < .05$
Bradycardia N (%)	4 (12.5%)	6 (17%)	N.S.
Paraesthesia N (%)	0°	5 (14%)	$p < .05$

Results are given as: number of patients (percentage) or mean ± SD. Mann-Whitney: $p < .05$; post-hoc χ^2 test: ° $p < .05$ vs Group $L_{0.5}$.

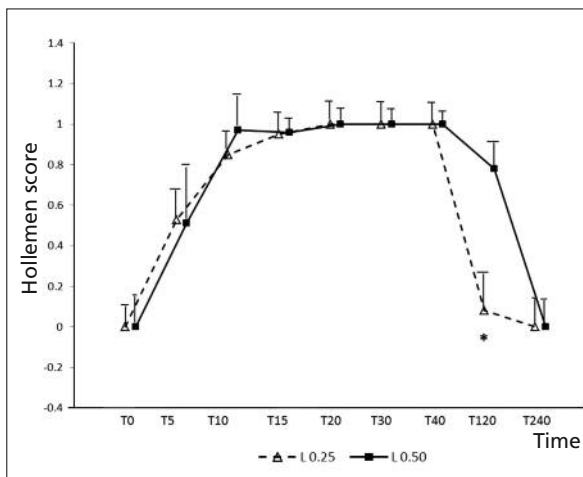


Figure 2. Time course of the Hollmen simplified scale in the two groups (open circles = Group $L_{0.25}$ and closed squares = Group_{control}). Two-ways ANOVA: $p < .01$; post-hoc Fisher exact test: $^{\circ}p < 0.05$ Group_{CONTROL} vs Group $L_{0.25}$).

(17%) patients in Group_{control}, and 4 (11%) patients in Group $L_{0.25}$ (NS) (Table I).

No patients experienced nausea or post dural puncture headache (Table I).

All patients expressed satisfaction with their intraoperative medication regimen (verbal rating scale score > 2), and expressed a willingness to receive the same technique again in the future. In addition, surgeons reported that they had been highly satisfied with the intraoperative conditions allowed by the anaesthesia technique.

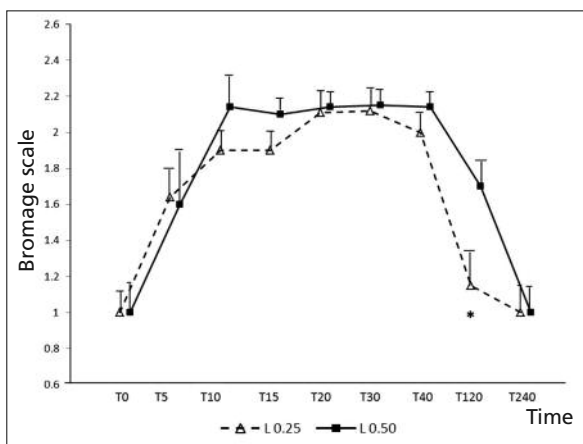


Figure 3. Time course of the Bromage scale (open circles = Group $L_{0.25}$ and closed squares = Group_{control}). Two-ways ANOVA: $p < .01$; post-hoc Fisher exact test: $p < .05$ Group_{control} vs Group $L_{0.25}$).

Discussion

The main results of our study are that in patients undergoing a caesarean delivery with the Stark method, intrathecal anaesthesia with 7.5 mg isobaric levobupivacaine and 2.5 μ g sufentanil provided effective anaesthesia without significant side effects both at 0.50% and 0.25% concentrations, in every patients (25,27,28). In addition, this study demonstrates that the use of a more diluted local anaesthetic solution produced shorter times to two-segments regression and complete sensory recovery (25).

Modified Stark's Caesarean Delivery

The modified Stark technique is widely used to perform a caesarean delivery^{2,16,22}: it avoids to perform a classical laparotomy, but allow to enter the abdomen just by hands eliminating retractors or surgical sponges. Actually, because of its minimal invasiveness and simplicity it can be performed both in planned or in emergency delivery². Moreover, this method do cause less intra- and postoperative pain since the only manoeuvre that requires an higher level of anaesthesia is the exteriorization of the uterus: when this is performed rapidly, as with the modified Stark method, not only the pain stimulation is reduced but also blood sequestration into the exteriorized uterus, with subsequent lower risk of hemodynamic instability. Additionally, the occurrence of postoperative pain is also reduced when peritoneum is not sutured, as in our patients. Nevertheless, even if a great variety of attempts have

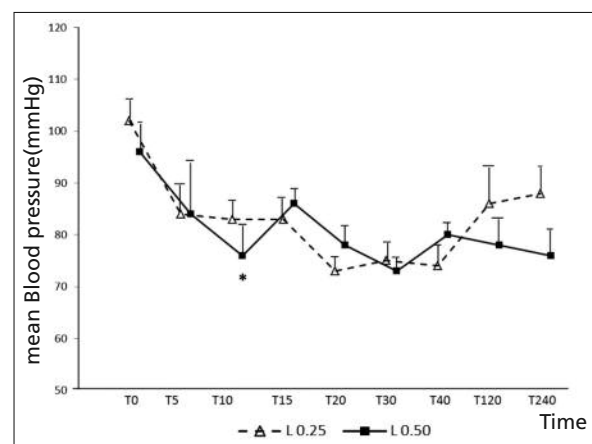


Figure 4. Time course of Blood pressure mean (open circles = Group $L_{0.25}$ and closed squares = Group_{control}). Two-ways ANOVA: $p < .01$; post-hoc Fisher exact test: $p < .05$ Group $L_{0.50}$ vs Group $L_{0.25}$).

been proposed in literature to improve the quality of spinal anaesthesia during caesarean delivery^{2,3,13,17}, the Stark CS has been poorly studied in terms of anaesthetic needs^{16,22}.

Block Intensity

Our data suggest that 7.5 mg of intrathecal levobupivacaine added with sufentanil was a sufficient dose to provide effective anaesthesia in every patient. Actually, dilution may not have a real effect on block intensity, while the dose-sparing effect of opioids added to intrathecal local anaesthetic solution is well known in literature^{23,24}, and contribute to the reduction of motor blockade degree as well as to the duration of effective analgesia in the perioperative period. Moreover, when using low local anaesthetic doses, the use of CSE technique is indicated, in order to allow for drug supplementation, in case of intraoperative²⁰.

Block Height

It is generally accepted that a sensory analgesia extended between the fourth and the sixth dermatome is necessary for Caesarean delivery¹³: in our patients a sensory block at or above the dermatome T6 was obtained in both groups, independently from solution's concentration. Actually, the cephalad spread of spinal blockade, may be influenced by patient's position, total milligram dose and baricity of the local anaesthetic solutions^{21,24,25}. In the present trial the levobupivacaine dose of 7.5 mg was constant in both study groups, while all patients were kept in sitting position during CSE positioning and intrathecal injection and placed in supine position thereafter. In literature hyperbaric solutions have for a long be considered more suitable to reach the thoracic dermatomes as opposed to their plain (i.e. isobaric) equivalents²⁶, because spinal anaesthesia with hyperbaric solutions is characterized by less individual variation in the cephalad spread of the block^{21,24-26}, although the upper level of sensory block is usually higher than with plain solutions. On the contrary, in obstetric patients the height of a spinal block may not differ when either plain or hyperbaric Levobupivacaine is used²⁷⁻²⁹, unlike non-obstetric patients. This can be explained by the presence of a lumbar lordosis typical of pregnant women: since iso/hypobaric solutions spread to non-dependent areas,

once the supine position is assumed the solution will redistribute toward the lumbar column and not towards the dorsal one, thus causing a low upper level of sensory block as hyperbaric solutions do because of their redistribution to dependent areas of the subarachnoid space^{20,30-33}. In our study, we used isobaric solutions^{6,20,27} that provided effective anaesthesia without significant side effects, since all women received a sensory block at or above the dermatome T6.

Block Duration

While concentration of 0.25% allowed a complete recovery from sensitive and motor block within 1 hour after the surgery, when using the 0.50% concentration, the cephalad spread of the solution occurred more often, and the recovery from sensitive and motor blockade was sensibly slower. Actually, early mobilization after Caesarean delivery is desirable, consequently a rapid recovery from motor blockade is important. In literature, in order to achieve adequate analgesia without excessive motor blockade, a combination of levobupivacaine at low concentration with other analgesic, such as an opioid, was suggested^{17,28}, since the addition of various doses of intrathecal opiates may allow the reduction of the local anaesthetic dose, with an equivalent success rate and less severe side effects. Synergistic effects allowing a reduction in dose of each drug have presumably played a role in the success rate of intrathecal anaesthesia in our patients²⁷.

As regards patients' safety, the first cause limiting the choice of spinal anaesthesia for Caesarean delivery is the possibility of neonatal cardiorespiratory depression, due to severe maternal hypotension caused by spinal anaesthesia: hypotension is common after spinal anaesthesia in parturients, partly due to cephalad spread of local anaesthetic in the subarachnoid space and also to aortocaval compression by the gravid uterus^{21,24,25}. In patients given 7.5-12.5 mg of 0.5% hyperbaric bupivacaine solution, an prevalence of hypotension equal to 24% and 26% respectively has been reported^{26,30}. In our study, the frequency of hypotension was less intense in Group_{L 0.25} than in Group_{control} ($p < 0.05$), probably due to the bigger cephalad spread in patients receiving L 0.50%. However, in no cases it was of clinical significance, while the reduction in heart rate observed in every patient on T_{120h} was probably due to the end of oxytocin's effect.

Conclusions

Although more data on local anaesthetic solution volume/dose/baricity relationship are needed our findings suggest that the levobupivacaine concentration may be reduced to 0.25% with a good quality anaesthesia for cesarean delivery performed with the Stark technique^{1,2}, since it is a comfortable technique with less hypotensive effects. We didn't observed differences in the occurrence of side effects and hemodynamic changes between groups, while the use of low concentration of levobupivacaine produced a progressively diminished intensity of motor blockade.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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