Full Length Research Paper

COMPARISON OF THE EFFECTS OF INTRATHECAL BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE IN LOWER ABDOMINAL SURGERY: A DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL USING ISOBARIC PREPARATIONS

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Abstract

Background: Though various local anesthetic agents are widely used intrathecally for lower umbilical surgeries, their efficacy vary even when used in equipotent doses.
Objective: The present study has been conducted to compare the efficacy of intrathecal bupivacaine, levobupivacaine and ropivacaine in lower umbilical surgery using isobaric preparations.
Study design: Double-blinded randomized controlled trial. Total 93 patients of ASA (American Society of Anesthesiologists) physical status I and II, all female, aged between 18 to 60 years, were randomized into 3 groups receiving 3 ml of 0.5% bupivacaine, 0.5% levobupivacaine and 0.75% ropivacaine in intrathecal route.
Results: Between bupivacaine and levobupivacaine groups, there was no significant difference in any parameter ($p>0.5$) but ropivacaine group had overall delayed onset and early recovery in several parameters.
Conclusion: Intrathecal bupivacaine and levobupivacaine showed superior efficacy. We recommend levobupivacaine owing to its safer cardiac profile.

Keywords: Bupivacaine, Levobupivacaine, Ropivacaine, Intrathecal Route, Lower Umbilical Surgery, Isobaric Preparations.

INTRODUCTION

Spinal anaesthesia (Subarachnoidanaesthesia SAB) is the most commonly used regional anesthesia technique today. It offers several advantages over general anesthesia (GA) like reduced morbidity, ability to use fewer drugs, ease of technique, having an awake patient and above all, avoidance of complications related to GA. But it also offers several disadvantages like hypotension, bradycardia, intraoperative discomfort (owing to an awake patient), post dural puncture headache and potential for neurologic and cardiologic toxicity from the local anesthetic agents used. Cocaine was the first spinal anesthetic used and procaine and tetracaine soon followed (Ruetsch *et al.*, 2001). Spinal anesthesia performed with lidocaine, bupivacaine, tetracaine, mepivacaine, and ropivacaine have been successful. Among them bupivacaine is one of the most widely used agent and provides adequate anesthesia and analgesia for intermediate to long duration surgeries (Frey *et al.*, 1998). But it has been associated with potentially fatal cardiotoxicity, especially with accidental intravascular administration. So, in this aspect, bupivacaine is less safe than other long acting local anesthetics like ropivacaine and levobupivacaine (Mather and Chang, 2006). Again, due to its high lipid solubility and protein bounding nature, bupivacaine is associated with central nervous system (CNS) toxicity as well (Liu *et al.*, 1983). Bupivacaine is a mixture of two enantiomers- R(+) and S(-). R(+) enantiomer is responsible for the toxicity of the local anesthetic agent (Hazra *et al.*, 2015). In

recent years, levobupivacaine, the pure S (-)-enantiomer of bupivacaine has thereby emerged as a safer alternative for regional anesthesia than its racemic parent. On the other hand, Ropivacaine is available as an optically pure S(-) enantiomer from the parent chiral molecule propivacaine. Levobupivacaine and bupivacaine produce comparable surgical sensory block with similar adverse effects and equal labor pain control with comparable maternal and fetal outcome (Burlacu and Buggy, 2008). In comparison with bupivacaine, following intravenous administration, levobupivacaine produces significantly less effects on cardiovascular function (Bardsley et al., 1998). Few studies show there is no significant difference between bupivacaine and levobupivacaine with respect to onset and duration of motor and sensory block and also the adverse effects (Sathitkarnmanee et al., 2011). Regarding baricity, hyperbaric levobupivacaine is more predictable for sensory block level and more effective for surgical procedures with lower abdominal approach.

Ropivacaine causes less CNS symptoms and is at least 25% less toxic than bupivacaine as per the dose tolerated by healthy volunteers (Scot et al., 1989). It has a lower systemic toxicity profile than levobupivacaine. Its better cardiotoxicity profile is an important advantage when using techniques with a potential for high plasma concentrations (Stienstra, 2000). However, as compared to bupivacaine, ropivacaine is found to be significantly less potent (by a factor of 0.4) when given to women in labour (Capogna et al., 1999). In India, ropivacaine (2009) and levobupivacaine (2012) were introduced much later than in other advanced countries. Both these preparations are isobaric in nature. Bupivacaine has both hyperbaric and isobaric preparations. Till date, literature search reveals only a few studies comparing bupivacaine with ropivacaine and levobupivacaine in equivalent doses in India. Hence, the present study was designed in a prospective, randomized, double-blind fashion to compare the effects of intrathecal bupivacaine, levobupivacaine and ropivacaine for patients undergoing lower abdominal surgery using isobaric preparations in equipotent doses.

MATERIALS AND METHODS

After approval from institutional ethical committee and obtaining written informed consent of the patients, the study was conducted in Medical College and Hospital, a tertiary care medical college hospital in eastern India. Total 93 patients of ASA (American Society of Anesthesiologists) physical status I and II, all female, aged between 18 to 60 years and scheduled for elective lower abdominal gynecological surgery, were enrolled in this study. Power calculations suggested that a minimum of 16 subjects per group were required to detect 30 minutes difference in mean duration of sensory anesthesia between groups [taking type I or α error of 5%, type II or β error of 20% and inter group standard deviation (SD) of 30 minutes, as shown in a previous study by Malinovsky et al., 2000. To be on a safer side, 31 patients were included in each group (n=31). Patients undergoing emergency surgery; having severe systematic disorders like stage-2 hypertension, diabetes, musculoskeletal, neurological disease etc.; those with history of drug and alcohol abuse; having previous abdominal surgery or presence of endometriosis, adhesion, tumors/carcinomas as pathological operative causes; allergic to amide local

anesthetics and those having body weight more than 30% of the ideal weight, were excluded from the study. Patients having contraindication to spinal anesthesia and those with inadequate block (defined as sensory block $< T_8$ segment), were also excluded from the study. Patients were admitted one day prior to the scheduled surgery and were examined and interviewed. Whole procedure was explained to the patients. On arrival in the operation theatre (OT), monitors were attached and baseline parameters like HR (heart rate), NIBP (non invasive blood pressure), SpO_2 (oxygen saturation), ECG (electrocardiogram) and temperature were recorded. Immediately before anesthesia, patients were randomly divided into three groups using sealed envelopes, as chosen by the patients.

The study groups were:

Group B: received 0.5% bupivacaine (i.e., 5 mg/ml).
Group L: received 0.5% levobupivacaine (i.e., 5 mg/ml).
Group R: received 0.75% ropivacaine (i.e., 7.5 mg/ml).

Total volume of the study drugs were adjusted to 3 ml.

Equivalent doses of bupivacaine (5 mg/ml), levobupivacaine (5 mg/ml) and ropivacaine (7.5 mg/ml) were calculated based on study by Lee et al., 2009, Gautier et al., 2003 and Malinovsky et al., 2000. The preservative-free isobaric preparations of these drugs were used. All patients were preloaded with 500 ml of Ringer's Lactate (RL) infusion and premedicated with 1 mg of midazolam and 75mcg of palanosetron intravenously. After skin's infiltration with 2% lidocaine, a 20G introducer Pitkin's needle was inserted at either L_3-L_4 or L_4-L_5 interspaces in the midline through which a 25G Whitacre needle was passed. After correct needle placement was identified (by free flow of cerebrospinal fluid) and confirmed (by aspiration), 3 ml of the study drug was injected over 15 seconds (Varun et al, 2012).

Drugs were drawn in similar syringes by a person not involved in the study as per random number allocated to the particular patient. Patient and the anesthesiologist administering the drug were thus blinded to the study preparation. The level of sensory block was evaluated by pinprick method using 20-gauge hypodermic needle. The test was performed every 5 minutes till loss of discrimination to pin prick for the first 15 minutes and thereafter every 10 minutes after operation until full recovery. Bilaterally T_{12}, T_{10}, T_8, T_6 or higher (T_4) dermatomes were checked by pin prick using forehead as baseline point for normal sensation. A decrease (regression) of at least 2 segments from maximum sensory block height was sought to allow the patients to be taken to the ward from PACU (post anesthesia care unit). Other criteria for post anesthesia discharge of patients to the ward were stable hemodynamics, absence of pain, vomiting or obvious bleeding etc. Motor blockade was assessed using a modified Bromage scale (0 = no motor block; 1= hip blocked; 2 = hip and knee blocked; 3 = hip, knee and ankle blocked). The time to reach maximum Bromage score (from spinal injection until Bromage 3 score) was taken as the onset time of motor block and was recorded every 5 minutes after injection of study drug for initial 15 minutes. Duration of analgesia was taken as the time from intrathecal injection to the time when the women first complained of pain and required supplemental analgesics.

Quality of surgical relaxation assessment was done by asking surgeons to grade their surgical exploration based on a 3 point grading scale (1 = poor, 2 = good, 3 = excellent). Hypotension was defined as arterial pressure lower than 25% of baseline and treated with injection phenylephrine intravenously in 100mcg increments. Bradycardia was defined as heart rate less than 50/min and treated with injection atropine intravenously in 0.6 mg increments. Hypoxia was defined as a decrease in SpO_2 to < 90% and treated with supplemental oxygen via a Hudson type polymask keeping FiO_2 (fraction of inspired oxygen) at 0.3 with a flow of 4 l/min.

Statistical Analysis

Data were expressed as mean and standard deviation (Mean ± SD). Normality of the distribution in each group was checked by the Shapiro-Wilk normality test. The homogeneity in 3 groups of mean and SD were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, Illinois, USA). Inter-group comparisons were done using one way analysis of variance (ANOVA). Post-hoc Tukey test was followed where ANOVA values were significant. Categorical data were compared using Chi-square test. A p value of less than 0.05 was considered as statistically 'significant' ($p < 0.05$) (Figure 1).

Table 1. Demographic profile (Mean ± SD)

Demographic profile	Group B	Group L	Group R	p value
Age (years)	45.47±9.94	48.63±10.93	47.17±13.77	0.578
Weight (Kg)	52.53±7.45	53.73±7.46	52.77±7	0.798
Height (cm)	147.3±8.9	150.53±8.13	147.3±11.03	0.314
BMI (Kg/m^2)	24±3.14	23.5±2.79	25.43±8.81	0.392
ASA (I : II)	21 : 9	17 : 13	21 : 9	0.456
Duration of surgery (min)	93.23±19.16	95.3±17.62	92.6±18.86	0.841

RESULTS

There were no significant differences between the three groups with regard to demographic data such as age, weight, height, BMI (body mass index), ASA grading and duration of surgery (Table 1). Comparison of three groups with regard to the block variables are shown in table 2. Between bupivacaine and levobupivacaine groups, there was no significant difference in any parameter. But, compared to the bupivacaine group, ropivacaine group had significantly delayed onset of sensory and motor block, but significantly shorter duration of motor
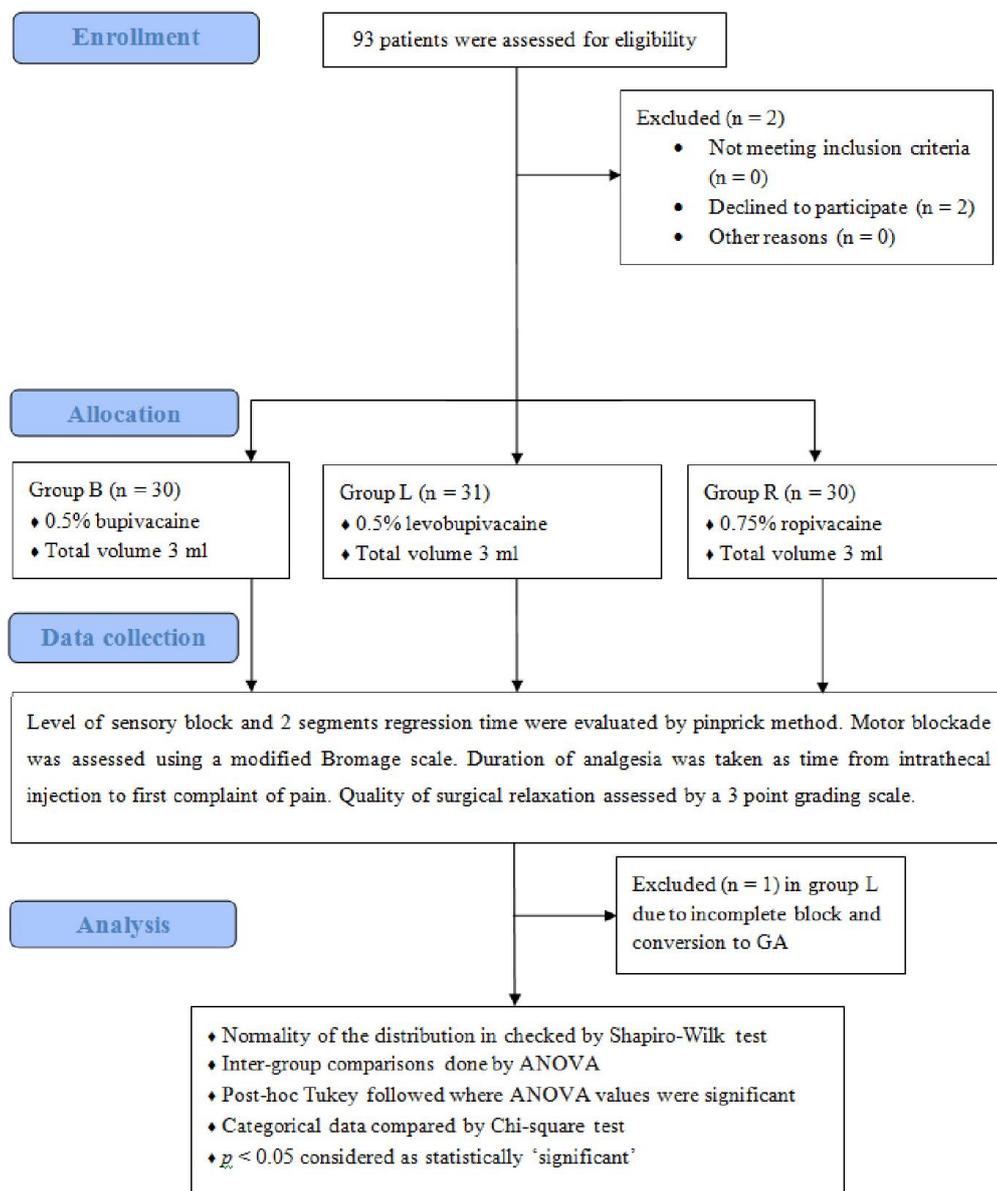

Figure 1. The CONSORT flow diagram of the study design

ropivacaine group had significantly delayed onset (both sensory and motor block), but significantly shorter duration (duration of anesthesia, analgesia as well as sensory and motor block), 2 segments regression time of sensory block and significantly less surgical relaxation score.

relaxation scores. When levobupivacaine and ropivacaine groups were compared, ropivacaine group had significantly delayed onset (both sensory and motor block), but significantly shorter duration (duration of anesthesia, analgesia as well as sensory and motor block), 2 segments regression time of

Table 2. Comparison of three groups with regard to block variables (Mean ± SD)

Block variables	Group B	Group L	Group R	p value
Duration of anesthesia (min)	140.03±30.48	149.63±27.82	130.2±24.73†	0.029
Onset of sensory block (min)	3.4±1.3	4.2±1.99	7.73±3.04*†	<0.001
Onset of motor block (min)	6.07±1.7	7.37±3.26	11.07±3.84*†	<0.001
Duration of sensory block (min)	135.83±30.86	145.43±28.21	122.47±25.4†	0.009
Duration of motor block (min)	144.37±25.33	159.6±29.54	124.57±25.53*†	<0.001
2 segments regression time of sensory block (min)	135.53±26.5	148.3±28.03	119.03±23.52*†	<0.001
Duration of analgesia (min)	140.03±26.46	154.2±27.72	127.87±21.97†	<0.001
Surgical relaxation score 1 : 2 : 3 (no. of patients)	0 : 3 : 27	0 : 8 : 22	0 : 18 : 12*†	0.001

Symbols represent a significant difference (p<0.05) compared with group B (*) or between group L and group R (†), as determined using a one-way ANOVA with a post-hoc Tukey test

Table 3. Comparison of three groups with regard to side effects

Side effects (no. of patients)	Group B	Group L	Group R	*p* value
Hypotension (present : absent)	8 : 22	3 : 27	6 : 24	0.252
Bradycardia (present : absent)	6 : 24	6 : 24	4 : 26	0.737

The three groups were comparable with regard to side effects profile *viz.*, hypotension and bradycardia (table 3).

DISCUSSION

This prospective observational cohort study was done to compare the effects of isobaric intrathecal injection of bupivacaine, levobupivacaine and ropivacaine in ASA 1 and ASA II patients who underwent lower abdomen surgery. They were randomly divided into 3 groups. Group B received 3ml (15mg) of 0.5% isobaric bupivacaine; group L received 3ml (15mg) of 0.5% isobaric levobupivacaine and group R received 3ml (22.5mg) of 0.75% isobaric ropivacaine. This study was done with the null hypothesis that equipotent doses of bupivacaine, levobupivacaine and ropivacaine will have similar onset, duration and quality of motor as well as sensory block along with hemodynamic stability. The dose of levobupivacaine and bupivacaine were found to be equipotent, but ropivacaine was found to be about two-third as efficacious of either bupivacaine or levobupivacaine as per the study of Lee *et al.*, 2009. We have thus chosen 5mg/ml concentrations of bupivacaine and levobupivacaine and 7.5mg/ml of ropivacaine in our study, keeping the volume constant. Malinovsky *et al.*, 2000 have also used 0.75% ropivacaine to compare with bupivacaine 0.5%. The demographic data of the patients with respect to age, body weight, height, BMI and ASA were comparable in both groups with no significant difference (*p*>0.05). We chose adult women aged between 18 to 60 years undergoing only lower abdominal gynecological surgeries to exclude maximum biases due to selection of patients and surgeries, and conform uniformity. The types of surgical cases performed were also similar with similar times for anesthesia and surgery in all the groups. On intergroup comparison, between bupivacaine and levobupivacaine groups, there was no significant difference in any parameter. But, compared to the bupivacaine group, ropivacaine group had significantly delayed onset of sensory and motor block, but significantly shorter duration of motor block, 2 segments regression time of sensory block and significantly less surgical

sensory block and significantly less surgical relaxation score. Thus, our initial null hypothesis that equipotent doses of bupivacaine, levobupivacaine and ropivacaine will have similar onset and duration of motor block, similar quality of motor and sensory block does not hold true for this study. The studies by Mantouvalou *et al.*, 2008 and Mehta *et al.*, 2007 with isobaric preparations of the same three drugs found delayed onset of sensory block in ropivacaine. Fattorini *et al.*, 2006 compared isobaric bupivacaine and levobupivacaine and found no significant difference regarding onset. However, Malinovsky *et al.*, 2000 found similar sensory onset time between isobaric bupivacaine and ropivacaine, which is different from our study. Mehta *et al.*, 2007 found that mean onset of motor block was significantly higher for ropivacaine than bupivacaine and levobupivacaine and there was no significant difference between bupivacaine and levobupivacaine. Mantouvalou *et al.*, 2008 compared intrahtecal 15 mg of isobaric bupivacaine, levobupivacaine and ropivacaine in patients undergoing lower abdominal surgery. They found similar onset time for motor block between levobupivacaine and ropivacaine but shorter onset of motor block with bupivacaine compared to either levobupivacaine or ropivacaine, which differs from our study. However, the findings by Fattorini *et al.*, 2006 support our study.

Mehta *et al.*, 2007 and Mantouvalou *et al.*, 2008 found that, the duration of sensory block was significantly shorter in patients receiving ropivacaine than in those receiving bupivacaine or levobupivacaine. However, Eryilmaz and Günaydın, 2011 found significantly longer duration of sensory block for ropivacaine than bupivacaine and levobupivacaine, which differ from our study. Mantouvalou *et al.*, 2008 and Mehta *et al.*, 2007 reported that ropivacaine had a shorter duration of motor block than bupivacaine and levobupivacaine, similar to our study. However, they found no significant difference in the duration of motor block among bupivacaine and levobupivacaine, which differs from our study. Turkmen *et al.*, 2012 compared anesthetic effects of intrathecal levobupivacaine and bupivacaine with fentanyl during

caesarean section and concluded that motor block time is longer with levobupivacaine than bupivacaine, a finding similar to our study. Varun *et al.*, 2012 in their study with isobaric bupivacaine and ropivacaine with fentanyl found longer duration of motor block of bupivacaine than ropivacaine, similar to our study. On the other hand, Malinovsky *et al.*, 2000 compared isobaric bupivacaine and ropivacaine and found no significant difference with duration of motor block among them, a finding different from our study. Erbay *et al.*, 2010 observed no significant difference between bupivacaine and levobupivacaine with 2 segment regression time of sensory block. Varun *et al.*, 2012 observed that the sensory block regression to S2 was faster in ropivacaine group as compared to bupivacaine group. All these support our study. On the contrary, Eryilmaz and Günaydın, 2011 concluded that ropivacaine has significantly longer 2 segment regression time of sensory block than bupivacaine. Mantouvalou *et al.*, 2008 concluded that isobaric preparation of ropivacaine had 2 segment sensory block regression time similar to isobaric bupivacaine or levobupivacaine, which also differs from our study.

Turkmen *et al.*, 2012 mentioned in their study that between bupivacaine and levobupivacaine, there was significant difference in duration of analgesia with a longer duration of analgesic effect of levobupivacaine, findings similar to our study. No significant difference between analgesic duration was found between bupivacaine and ropivacaine in the study by Chari *et al.*, 2013 similar to our study. On the contrary, Lim *et al.*, 2004 compared of duration of analgesia of intrathecal 2.5 mg of isobaric bupivacaine, ropivacaine, and levobupivacaine in combined spinal epidural analgesia for patients in labor and observed duration of analgesia is more with bupivacaine than levobupivacaine and ropivacaine. These findings were similar to another study by del-rio-Vellosillo *et al.*, 2014 which differ from our study. Eryilmaz *et al.*, 2011 calculated surgical satisfaction in terms of "very good", "good", "moderate", "bad" or "very bad". In their study comparing hyperbaric bupivacaine and levobupivacaine, surgical satisfaction was more with bupivacaine. Similarly, in the study by del-rio-Vellosillo *et al.*, 2014 surgical satisfaction was excellent in more patients receiving bupivacaine than levobupivacaine. These findings differ from our study. In our study the satisfaction rate of surgeons as "excellent" was significantly higher in bupivacaine and levobupivacaine group than in ropivacaine group ($p < 0.05$). Hypotension and bradycardia among patients in the three groups were comparable with no significant differences throughout the procedure ($p > 0.05$). Erbay *et al.*, 2010; Mehta *et al.*, 2007 and Chari *et al.*, 2013 support our findings. However, Varun *et al.*, 2012 observed that bupivacaine causes more incidences of hypertension when compared to ropivacaine. Kulkarni *et al.*, 2014 found that bupivacaine causes more incidences of hypertension than levobupivacaine.

Limitation of Study

Our study suffered from several limitations. Firstly, there was no control group in this study. Secondy, we were bound to do the study with isobaric prepatations of bupivacaine, levobupivacaine and ropivacaine, as no hyperbaric prepatation of levobupivacaine and ropivacaine are available commercially in our country till date. Thirdly, equipotency of the drug was calculated arbitrarily. Few studies are available regarding the equivalent dose of bupivacaine, levobupivacaine and ropivacaine. Also like all study conducted in a double blind technique, there is chance of inherent biases as well as, inter-observer variation in measuring various block characteristic and data recording. We did not measure the peak onset of either motor or sensory block, because surgical procedure started after onset of sensory and motor blockade. The quality of sedation or incidences of nausea and vomiting were also not studied during the intraoperative and postoperative period. We also failed to note the time to micturition, mobilization or return of bowel movement of our patient.

Conclusion

In our double-blind randomized controlled trial, administration of intrathecal bupivacaine and levobupivacaine showed superior efficacy in terms of sensory and motor block, analgesia and surgical relaxation, when compared with ropivacaine in lower abdominal surgery. We recommend routine use of 0.5% levobupivacaine in intrathecal route owing to its better cardiac profile. Further, larger trials are needed to confirm our findings.

Acknowledgements

REFERENCES

Bardsley, H., Gristwood, R., Baker, H., Watson, N. and Nimmo, W. 1998. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol., 46: 245-49.

Burlacu, C. and Buggy, D. 2008. Update on local anesthetics: focus on levobupivacaine. Ther Clin Risk Manag., 4(2): 381–92.

Capogna, G., Celleno, D., Fusco, C., Lyons, G. and Columb, M. 1999. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Brit J Anaesth., 82(3): 371-3.

Chari, V., Goyal, A., Sengar, P. and Wani, N. 2013. Comparison between intrathecal isobaric ropivacaine 0.75% with hyperbaric bupivacaine 0.5%: A double blind randomized controlled study. Anaesth Pain & Intensive Care., 17(3): 261-6.

del-Rio-Vellosillo, M., Garcia-Medina, J., Abengochea-Cotaina, A., Pinazo-Duran, M. and Barbera-Alacreu, M. 2014. Spinal Anesthesia for Knee Arthroscopy Using Isobaric Bupivacaine and Levobupivacaine: Anesthetic and Neuroophthalmological Assessment. BioMed Res Int., 349034.

Erbay, R., Ermumcu, O., Hanci, V. and Atalay, H. 2010. A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: A randomized controlled trial. Minerva Anestesiol., 76(12): 992-1001.

Eryilmaz, N. and Günaydın, B. 2011. A comparison of the effects of intrathecal ropivacaine and bupivacaine during cesarean section. Turk J Med Sci., 41(2): 219-226.

Fattorini, F., Ricci, Z., Rocco, A., Romano, R., Pascarella, M. and Pinto, G. 2006. Levobupivacaine versus racemic bupivacaine for spinal anaesthesia in orthopaedic major surgery. Minerva Anestesiol., 72(7-8): 637-44.

Frey, K., Holman, S., Mikat-Stevens, M., Vazquez, J., White, L., Pedicini, E., *et al*. 1998. The recovery profile of hyperbaric spinal anesthesia with lidocaine, tetracaine, and bupivacaine. Reg Anesth Pain Med., 23(2): 159-63.

Gautier, P., Kock, M., Huberty, L., Demir, T., Izydorczic, M. and Vanderick, B. 2003. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. Brit J Anaesth., 91(5): 684-9.

Hazra, R., Manuar, M.B., Manjunatha, S.M., Chakraborty, S., Ghosh, K., Basu, R., *et al*. 2015. Analgesic effects of intra-articular ropivacaine following arthroscopic knee surgery: Results of a double-blind, randomized controlled trial between two different doses. Asian J Med Sci., 6(1): 81-6.

Kulkarni, K., Deshpande, S., Namazi, I., Singh, S. and Kondilya, K. 2014. A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia. J Anaesthesiol Clin Pharmacol., 30(2): 238-42.

Lee, Y., Kee, W., Fong, S., Liu, J. and Gin, T. 2009. The Median Effective Dose of Bupivacaine, Levobupivacaine, and Ropivacaine After Intrathecal Injection in Lower Limb Surgery. Anesth Analg., 109: 1331-4.

Lim, Y., Ocampo, C. and Sia, A. 2004. A comparison of duration of analgesia of intrathecal 2.5 mg of bupivacaine, ropivacaine, and levobupivacaine in combined spinal epidural analgesia for patients in labor. Anesth Analg., 98(1): 235-9.

Liu, P., Feldman, H., Giasi, R. and Patterson, M. 1983. Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg., 62(4): 375-9.

Malinovsky, J., Charles, F., Kick, O., Lepage, J., Malinge, M., Cozian, A., *et al*. 2000. Intrathecal anesthesia: ropivacaine versus bupivacaine. Anesth Analg., 91(6): 1457-60.

Mantouvalou, M., Ralli, S., Arnaoutoglou, H., Tziris, G. and Papadopoulos, G. 2008. Spinal anesthesia : Comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. Acta Anaesth., 59: 65-71.

Mather, L. and Chang, D. 2006. Cardiotoxicity with modern local anaesthetics: is there a safer choice? Drugs., 61(3): 333-42.

Mehta, A., Gupta, V., Wakhloo, R., Gupta, N., Gupta, A., Bakshi, R., *et al*. 2007. Comparative evaluation of intrathecal administration of newer local anaesthetic agents Ropivacaine and Levobupivacaine with Bupivacaine in patients undergoing lower limb surgery. Internet J Anesthesiol., 17: 17.

Ruetsch, Y., Böni, T. and Borgeat, A. 2001. From cocaine to ropivacaine: the history of local anesthetic drugs. Curr Top Med Chem., 1(3): 175-82.

Sathitkarnmanee, T., Thongrong, C. and Tribuddharat, S. 2011. A comparison of spinal isobaric levobupivacaine and racemic bupivacaine for lower abdominal and lower extremity surgery. J Med Assoc Thai., 96(4): 716-20.

Scot, B., Lee, A., Fagan, D., Bowler, G., Bloomfield, P.and Lundh, R. 1989. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg., 69: 563-9.

Stienstra, R. 2003. The place of ropivacaine in anesthesia. Acta Anaesth. Belg., 54: 141-8.

Turkmen, A., Moral, D.A., Ali, A. and Altan, A. 2012. Comparison of the anesthetic effects of intrathecal levobupivacaine + fentanyl and bupivacaine + fentanyl during caesarean section. Middle East J Anaesthesiol., 21(4): 577-82.

Varun, S., Srivastava, M., Maurya, I., Garg, R., Dhama, V. and Manik, Y. 2012. A clinical prospective, randomized study to compare intrathecal isobaric bupivacaine – fentanyl and isobaric ropivacaine – fentanyl for lower abdominal and lower limb surgeries. Anaesth Pain & Intensive Care., 16(3): 237-42.

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