

A Comparative Study of Intrathecal Low dose Isobaric and Hyperbaric Levobupivacaine in Ambulatory Perianal Surgeries: A Prospective, Double Blind Study

Swathi Nagaraja¹, SS Nethra², Bhargavi Sanket³, Mamatha Chikkanarasimha⁴, NV Vani⁵

^{1,3}Assistant Professor, ²Professor, ^{4,5}Senior Resident, Department of Anaesthesiology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka 560002, India.

Abstract

Background: Perianal surgeries can be conveniently performed under saddle block. We intended to compare intrathecal low dose isobaric and hyperbaric levobupivacaine and study their efficacy in perianal surgeries under saddle block on ambulatory basis.

Methods: In this prospective, randomised controlled, double blind trial involving 20 patients in each group were randomised into two groups, Group I and Group H. Group I received 1ml of 0.5% levobupivacaine (5 mg) + 0.16 ml of Normal Saline (total volume-1.16 ml) and Group H: 1 ml of 0.5% levobupivacaine (5 mg) + 0.16 ml of 50% dextrose (total volume-1.16 ml). Duration for ambulation being the primary criteria, we also noted maximum cephalic spread, time to reach maximum height of sensory blockade, 2 segment regression, duration of motor and sensory blockade, time for voiding and time for rescue analgesia. Appropriate statistical tests were used for final analysis. P value less than 0.05 was considered statistically significant.

Results: There were no significant differences between the two groups in terms of the maximum height of sensory blockade and 2 segment regression that was achieved and request for first rescue analgesic. Duration of motor blockade, time to full recovery of sensory block and first voiding were all statistically significantly shorter in group H than group I.

Conclusions: We conclude that hyperbaric levobupivacaine is superior to isobaric form while being closer to ideal choice of anaesthetic agent on ambulatory basis required for perianal anaesthesia while both the concentrations are similar in their safety profile.

Keywords: Ambulatory; hyperbaric; Intrathecal; Isobaric; Levobupivacaine; Perianal.

How to cite this article:

Swathi Nagaraja, SS Nethra, Bhargavi Sanket et al. / A Comparative Study of Intrathecal Low dose Isobaric and Hyperbaric Levobupivacaine in Ambulatory Perianal Surgeries: A Prospective, Double Blind Study. Indian J Anesth Analg. 2021;8(1):89-95.

Introduction

Perianal surgeries are common procedures performed in the ambulatory setting. The primary

goals are to reduce anaesthetic complications and to allow for early patient discharge. Saddle block is a preferred technique for perianal surgeries as it produces analgesia, anaesthesia, and motor

Corresponding Author: Bhargavi Sanket, Assistant Professor, Department of Anaesthesiology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka 560002, India.

E-mail: swathisaggi@gmail.com

Received on 25.12.20, Accepted on 13.02.2021.



This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0.

block only in the perianal area.¹ However, this effect depends upon the volume, concentration, and doses of the drug used. Although hyperbaric local anaesthetic solutions like 0.5% hyperbaric bupivacaine have a remarkable record of safety, their use is not totally without risks. Hyperbaric solutions may cause hypotension or bradycardia after mobilization.²

Levobupivacaine, the S-enantiomer of racemic bupivacaine, is equipotent with bupivacaine when used in a similar concentration and dose. At the same time, levobupivacaine has lesser cardiac and central depressant action due to its faster protein binding rate.³⁻⁶ Both hyperbaric levobupivacaine and isobaric levobupivacaine have been used in anorectal surgeries.⁷ However, there are not enough data, whether one form is superior to the other.

We intended to compare intrathecal low dose isobaric and hyperbaric levobupivacaine and study their efficacy in perianal surgeries under saddle block on ambulatory basis.

Material and Methods

Patients undergoing anorectal surgeries for various ailments were included in the study after taking informed consent in this prospective randomised controlled, double blind trial. The study was performed under the Tenets of the Declaration of Helsinki after obtaining clearance from the hospital ethics committee and registration in Clinical trial registry bearing reference number CTRI/2020/09/027982.

Patients belonging to American Society of Anesthesiologists (ASA) physical status I and II, age between 18 to 50 years of either sex and done on elective anorectal surgeries (fistulectomy, fissurectomy, haemorrhoidectomy, lateral internal sphincterotomy, perianal sinus, perianal abscess incision and drainage) were included in the study. Patients with diabetes and hypertensive status, previously on alpha agonists, steroids, antidepressants, any contra indication for neuraxial regional techniques, patient refusal and those with history of drug allergies were excluded from the study.

Patients were randomly allocated using computer generated randomisation (www.random.org) into 2 groups. Group I received 1ml of 0.5% levobupivacaine(5 mg) + 0.16 ml of Normal Saline in tuberculin syringe (total volume-1.16 ml) and Group H : 1 ml of 0.5% levobupivacaine(5 mg) + 0.16 ml of 50% Dextrose in tuberculin syringe(total

volume-1.16 ml).

Pre anesthetic examination comprised of detailed history and systemic and airway examination. Preoperative investigations were done. All the patients were kept fasting for eight hours prior to surgery. Premedication with oral ranitidine hydrochloride 150 mg and alprazolam 0.25 mg given the night before the surgery.

Before surgery, patients were given instructions to use a 10-point Visual analogue scale (VAS) with 0 indicating no pain and 10 indicating the worst imaginable pain. In the operating room, electrocardiogram, pulse oximetry and non-invasive blood pressure (BP) were monitored, and baseline values recorded. All the patients were premedicated with Inj. Midazolam 1 mg IV. Following infusion of 500 ml lactated Ringer's solution, with the patient in the sitting position under aseptic precautions, lumbar puncture performed at L3-L4 interspace or L4-L5 interspace using 26 gauge spinal needle. The randomisation and loading of study drugs was done by a senior anaesthesiologist who was not involved further in the study. Just before spinal anaesthesia, syringe was handed over to the anaesthesiologist performing the subarachnoid block, who also monitored the patient subsequently. Thus, both the observer and the patient were blinded to the study drugs. The anaesthesiologist monitoring the patient intraoperatively and post operatively were not aware of the group allocation.

After intrathecal injection of drug, patients were made to sit for ten min, after which patients were placed in supine position. Intraoperatively heart rate, systolic BP, diastolic BP and mean arterial pressure, oxygen saturation and respiratory rate were recorded every 2 min for first 10 min then every 5 min till end of procedure. The sensory block level was assessed using cold swab for temperature discrimination along the midclavicular line and lateral part of dorsum of foot (S1) and perianal area. Motor level checked using Breen's Modification of Bromage scale. Sensory and motor block levels were noted after completion of 5 min when the patient was made supine and then every 2 min until the start of surgery. Maximum height of sensory block achieved was noted. If patient complained of pain during surgery, it was considered as failure of subarachnoid block and general anaesthesia instituted. Patients requiring general anaesthesia were not included for statistical analysis.

Post-operatively, Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), oxygen saturation (SPO2), Visual analogue

scale (VAS), sensory and motor levels were noted in immediate post-operative period and then 15 min in the first post-operative hour and then, every half hourly till next two hours, then every hourly till 6 hours or till patient was ambulated . Patient made ambulant when the following criteria were achieved (1) Able to perform partial knee bend (Bromage scale 6) (2) recovery of proprioception of great toe (3) return of perianal sensation (4) no postural hypotension on making the patient stand . Time for ambulation(primary criteria) was recorded from the time of SAB to the time when patient was made ambulant . Time for urination and side effects if any were also observed in the post-operative period. Side effects such as hypotension (defined as a decrease in mean arterial pressure >25% of the baseline value) treated with IV boluses of 6 mg ephedrine. Bradycardia defined as a pulse rate of <50 beat/min was treated with bolus of 0.6 mg atropine IV, Respiratory depression (RR <8 or SpO2 <95%) treated with oxygen supplementation and respiratory support if required, vomiting and others if any were noted.

Sample size

The sample size was calculated based on observations from previous studies.⁸ Keeping the power of study as 80% and α error as 5% , to detect at least 15% difference in time to ambulation between two groups hypothesizing isobaric levobupivacaine causing better ambulation, a minimum of 17 patients is required in each group . For a better validation of results, we included 20 patients in each group . The patients were randomly

allocated into two groups of 20 each using computer generated randomization .

Results

A total of 42 adult patients were assessed for eligibility. One patient in Group H had technical failure of subarachnoid block and another patient had a complex fistula and hence duration of surgery was prolonged. Both were converted to general anaesthesia. They were excluded from statistical analysis. 20 patients in each group was randomly assigned using computer generated randomisation to one of two treatment groups [Fig 1].

The two groups were comparable with respect to age, gender, weight, height, ASA physical status type and duration of surgical procedure [Table 1] .

The maximum median cephalic sensory blockade levels achieved were S1 (L3- S2 interquartile range) and T12(L1- T10 interquartile range) in groups H and I, respectively. There were no significant differences between the two groups in terms of the maximum height of sensory blockade and 2 segment regression that was achieved. Duration of motor blockade, time to full recovery of sensory block, first voiding and time for ambulation were all statistically significantly shorter in group H than group I [Table 2]. There were no significant differences in the number of episodes of hypotension, bradycardia, nausea,vomiting, headache or respiratory depression requiring treatment between the two groups. In addition, time for request of first rescue analgesic was not statistically significant between the two groups.

Table 1: Demographic details, type and duration of surgery SD-Standard Deviation; min-minutes.

| | Hyperbaric | Isobaric | P value |
|-----------------------------------------|----------------|-----------------|---------|
| Age (in years), mean \pm SD | 38.3 \pm 4.2 | 40.2 \pm 3.0 | 0.10 |
| Male:Female | 8:12 | 10:10 | |
| ASA physical status(I:II) | 15:5 | 13:7 | |
| Type of surgery | | | |
| Fistulectomy | 6 | 4 | |
| Fissurectomy | 4 | 4 | |
| Haemorrhoidectomy | 4 | 6 | |
| Lateral internal sphincterotomy | 3 | 4 | |
| Perianal sinus | 1 | 2 | |
| Perianal abscess incision and drainage | 2 | Nil | |
| Duration of surgery(min), mean \pm SD | 46.5 \pm 7.7 | 50.40 \pm 6.2 | 0.08 |

Table 2: Comparison of various parameters between the hyperbaric and isobaric group along with the p-value. P-value ≤ 0.05 was considered to be statistically significant; min-minutes.

| | Group H (mean ± SD) | Group I (mean ± SD) | p-value |
|----------------------------------------------------|---------------------|---------------------|---------|
| Time to reach max height of sensory block (in min) | 11.1± 2.6 | 12.0 ± 3.4 | 0.26 |
| 2 segment regression (in min) | 61.2± 4.3 | 59.3± 3.2 | 0.19 |
| Duration of motor blockade (in min) | 127.6± 8.6 | 165.3± 9.1 | 0.0001 |
| Full recovery sensory block (in min) | 175.6± 13.2 | 198.6± 17.6 | 0.001 |
| Time for ambulation (in min) | 172±12.1 | 189±10.2 | 0.001 |
| Time for first voiding (in min) | 274± 28.4 | 309.6± 40.5 | 0.03 |
| Time for rescue analgesia (in min) | 228.6± 16.5 | 230.1± 14.4 | 0.76 |

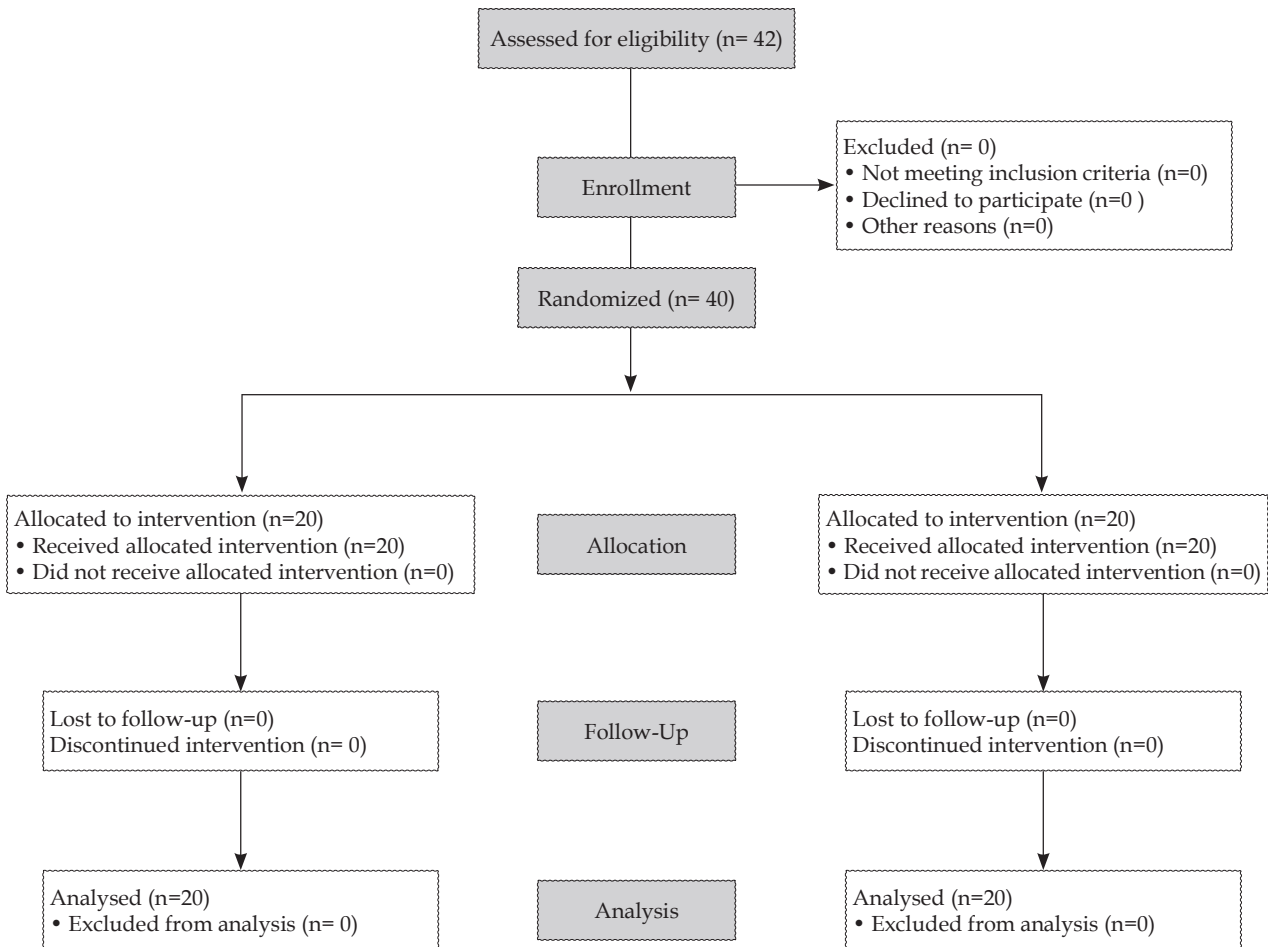


Fig. 1: Consort Flow Diagram.

Table 3: Frequency of adverse effects.

| Adverse effects | Group H (n= 20) | Group I (n=20) | P value |
|-------------------|-----------------|----------------|---------|
| Hypotension | 1 | 2 | 0.5775 |
| Bradycardia | - | - | - |
| Nausea | - | - | - |
| Vomiting | - | - | - |
| Headache | - | - | - |
| Urinary retention | - | - | - |

Discussion

Our study compared block characteristics, clinical effects and complications of two different baricities of constant dose intrathecal levobupivacaine.

The effect of isobaric local anaesthetics has been not been consistent as shown in few studies. Levobupivacaine is available commercially in isobaric form. We prepared different baricity of levobupivacaine by adding 80 mg (0.16 ml) of 50% dextrose to isobaric levobupivacaine.

According to previous studies, limiting spinal block only to the dermatomal extent of the operative site provides better cardiovascular stability, faster motor and sensory recovery. Small doses of long-acting local anaesthetics have been used to obtain short-lasting spinal block.⁹

The ideal agent for day-case anaesthesia produces a rapid onset of a reliable block providing adequate surgical anaesthesia of appropriate duration and followed by a rapid regression of the motor and sensory blocks with minimal side-effects allowing rapid recovery and subsequent quicker hospital discharges.¹⁰

Smaller doses like 5-10 mg can be used in ambulatory surgeries. At such low concentrations, it produces a differential neuraxial block with preservation of motor function. The minimum local anaesthetic dose (MLAD) of intrathecal levobupivacaine is 5.68 mg for lower limb surgery.^{3,4,11,12}

Naithani et al compared hyperbaric bupivacaine with isobaric levobupivacaine in lower limb orthopaedic surgeries, and found that although onset of sensory and motor block was significantly rapid, duration of sensory block was significantly longer in bupivacaine group as compared to levobupivacaine group. They proved that isobaric levobupivacaine offered effective clinical characteristics with stable hemodynamics and significantly decreased cardiovascular and central nervous system toxicity, so they concluded levobupivacaine to be a suitable alternative to

hyperbaric bupivacaine in spinal anaesthesia.²

Sen et al also performed a similar study and proved that hyperbaric levobupivacaine had a faster onset of sensory and motor block with shorter duration of sensorimotor block than the isobaric form.⁸ Similarly, in our study the onset was hastened and duration of block was longer in hyperbaric group than isobaric group but there was no difference in duration of analgesia between the two groups. Gulen G et al compared isobaric levobupivacaine with hyperbaric bupivacaine in caesarean section. In their study, time to reach maximum motor block in isobaric levobupivacaine was 11.36±2.35 min and in hyperbaric levobupivacaine was 6.13±1.56 min. We have obtained similar results. Few reviews have commented that use of hyperbaric levobupivacaine results in more predictable cephalad spread, also prolongs the duration of block, and also leading to a more rapid sensory and motor recovery.^{4,12}

In the study by Alka Verma et al, in Group in which 50 mg dextrose was added to 7.5 mg levobupivacaine, 2 segment regression time was 49.2±3.09 min, which was significantly shorter than the times of other groups with 75 mg and 100 mg dextrose (56.76±3.68, 59.08±4.17).¹⁴ Two segment regression in our study in hyperbaric group was 61.2±4.3 min whereas in isobaric group 59.3±3.2 min but the difference was not statistically significant.

In our study, the highest level of sensory blockade was seen in isobaric group reaching upto T12 whereas it remained confined to the site surgery in hyperbaric group reaching maximum L1 level. In the study by Sananlip et al, in which they studied characteristics of isobaric and hyperbaric levobupivacaine in gynaecological surgeries, isobaric levobupivacaine caused a wider range of peak levels (L1 to C8) compared with hyperbaric form (T7 to T2). They suggested that hyperbaric levobupivacaine had more predictable sensory block 3. Similar maximum sensory block heights were also found in study comparing hyperbaric and hypobaric levobupivacaine in unilateral spinal anaesthesia for elective ambulatory arthroscopic surgery of the knee by Kaya et al.⁹ Few other studies did not notice any difference between the two groups in maximum height achieved when they compared isobaric levobupivacaine with hyperbaric solutions.^{8,15} This difference may be due to the varying properties of drugs, their reaction to gravity and the movement of CSF due to postural changes. Gravity tends to keep the hyperbaric solution near the lowest point of the thoracic curve (T4/T5) in the supine position and preventing the flow further in a cranial direction.

This tendency to spread could be further increased with the viscosity of the hyperbaric solution, and prevent it mixing with the CSF. The plain solution, mixes freely with CSF, has neither gravitational nor viscous effect to restrict its movement within the displaced CSF and can spread unexpectedly high even after a reasonable time for fixation causing late complications like hypotension and bradycardia.^{3,15,16}

Hyperbaric and hypobaric levobupivacaine both provided unilateral spinal anaesthesia more frequent in the hyperbaric group with good haemodynamic stability for arthroscopic surgery, in the study by Kaya et al.⁹ Strictly unilateral sensory block was present in 30 min after injection (P = 0.40), and unilateral motor block was observed in 94%, 93%, and 83% in groups Ropi-7.5, Levo-7.5, and Levo-5, respectively (P = 0.31) in yet another study by Capellari et al.¹⁷

We found that time to achieve maximum sensorial blockade was prolonged in isobaric group compared to hyperbaric group though it was not statistically significant (12.0 ± 3.4 vs 11.1 ± 2.6 min, $p = 0.26$). In the study by Ozgur et al, time for sensorial block to achieve T12 level was slower (12.5 ± 2.2 min) in group containing less dextrose.¹⁸ In contrast, Sasanlip et al found that hyperbaric levobupivacaine, compared with isobaric levobupivacaine, spread faster to T10 level (2.8 ± 1.1 versus 6.6 ± 4.7 minutes, $P = 0.039$).³ Ajay Singh et al observed no difference in the block onset time or maximum block height.¹⁵

We found no difference in duration of analgesia between the two groups (228.6 ± 16.5 vs 230.1 ± 14.4 min, $p = 0.76$). Ajay Singh et al compared isobaric levobupivacaine with hyperbaric racemic bupivacaine in patients undergoing inguinal hernia surgery. The duration of anaesthesia was significantly shorter in group L compared with that in group B (206.2 ± 18.9 min vs. 224.1 ± 15.6 min, $P < 0.001$).¹⁵

With regards to full recovery of sensory block and duration of motor blockade, both were statistically significant (175.6 ± 13.2 vs 198.6 ± 17.6 min, $p < 0.01$; 127.6 ± 8.6 vs 165.3 ± 9.1 min, $p < 0.001$) being prolonged in isobaric group. Ozgur et al., in the group containing 80 mg dextrose, time to full recovery of sensory block was 154 min and duration of motor block was 105 min, both increasing with increase in density of levobupivacaine.¹⁸ Kaya et al found that duration of sensory block although similar, motor block regression was faster in the hyperbaric group compared to hypobaric

group.⁹ This is due faster clearance of unbound levobupivacaine compared with plain bupivacaine represented by faster waning of the sensory block with levobupivacaine, duration of motor block being 185.9 ± 20.3 min as explained by Ajay Singh et al.¹⁵ Also, time for ambulation was significantly faster in group H compared to group I in our study.

We have found statistically significant difference in time for first voiding being 274 ± 28.4 in hyperbaric group vs 309.6 ± 40.5 min in the isobaric group ($p = 0.03$). In the study by Ozgur et al, in Group I containing 60 mg dextrose was statistically significantly shorter than in the other groups containing 80 mg and 100 mg dextrose ($p < 0.001$).¹⁸ Rapid return to bladder function is due to unilateral blocking of the sacral parasympathetic efferent ligaments innervating the detrusor muscle.

The incidence of hypotension was less in group Levobupivacaine (12%) compared to group Bupivacaine (32%) ($P = 0.028$) in the study by Ajay Singh et al.¹⁵ The difference in results can be attributed to the difference in the dose or baricity of the drugs used according to the nature of the surgery. Even in our study, all patients were hemodynamically stable and no significant difference was found in either of the groups. Herrera et al in their observational pilot study assessed the hemodynamic impact, hemoglobin and oxygen saturation of isobaric levobupivacaine versus hyperbaric bupivacaine for subarachnoid anesthesia in geriatric patients undergoing hip surgery. They observed lower incidence of intraoperative hypotension even in elderly.¹⁹

The main limitation of our study is that we did not compare time to mobilisation and actual discharge they may be affected by patient or surgery-related factors that are independent of the anaesthesia. The main issue with levobupivacaine is that hyperbaric formulations are not available commercially, so we have to alter their baricity. This can potentially diminish spinal injection sterility and safety. Also, final anaesthetic solution density is less predictable than that of commercially available hyperbaric formulations.

To summarise, our results show that levobupivacaine with dextrose making it hyperbaric has significantly lesser duration of motor blockade, recovers from sensory blockade quite early and time for first urination being lesser compared with isobaric bupivacaine. None of the two groups being superior with regard to time for first rescue analgesic.

Conclusions

We conclude that hyperbaric levobupivacaine is superior to isobaric form while being closer to ideal choice of anaesthetic agent on ambulatory basis required for perianal anaesthesia while both the concentrations are similar in their safety profile.

References

1. Wassef MR, Michaels EI, Rangel JM, Tsyrlin AT. Spinal perianal block: a prospective, randomized, double-blind comparison with spinal saddle block. *Anesth Analg* 2007;104:1594-6.
2. Gulen Guler, Gokhan Cakir, Ayşe Ulgey, Fatih Ugur, Cihangir Bicer, Isin Gunes, Adem Boyaci. A Comparison of Spinal Anesthesia with Levobupivacaine and Hyperbaric Bupivacaine for Cesarean Sections: A Randomized Trial. *Open Journal of Anesthesiology*, 2012;2:84-89.
3. Sanansilp V, Trivate T, Chompubai P, Visalyaputra S, Suksopee P, Permpolprasert L, von Bormann B. Clinical characteristics of spinal levobupivacaine: Hyperbaric compared with isobaric solution. *ScientificWorldJournal*. 2012;2012:169076.
4. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review. *J Anaesthesiol Clin Pharmacol*. 2013;29:530-9.
5. Athar M, Ahmed SM, Ali S, Siddiqi OA. Levobupivacaine: A safer alternative. *J Curr Res Sci Med*. 2016;2:3-9.
6. Erdil F, Bulut S, Demirbilek S, Gedik E, Gulhas N, Ersoy MO. The effects of intrathecal levobupivacaine and bupivacaine in the elderly. *Anaesthesia* 2009;64:942-6.
7. Kazak Z, Ekmekci P, Kazbek Z. Hyperbaric levobupivacaine in anal surgery: Spinal perianal and spinal saddle blocks. *Anesthetist*. 2010;59:709-13.
8. Kaya M, Oztürk I, Tuncel G, Senel GO, Eskiçirak H, Kadiogullari N. A comparison of lo dose hyperbaric levobupivacaine and hypobaric levobupivacaine in unilateral spinal anaesthesia. *Anaesth Intensive Care*. 2010;38:1002-7.
9. Luck JF, Fettes PDW, Wildsmith JAW. Spinal anaesthesia for elective surgery: a comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine. *Br J Anaesth* 2008;101:705- 10.
10. Lee YY, Ngan Kee WD, Fong SY, Liu JT, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. *Anesth Analg* 2009;109:1331-4.
11. Del-Rio-Vellosillo M, Garcia-Medina JJ, Pinazo-Duran MD, AbengocheaCotaina A. Doses and effects of levobupivacaine and bupivacaine for spinal anaesthesia. *Br J Anaesth* 2014;113:521-2.
12. Sen H, Purtuloglu T, Sizlan A, Yanarates O, Ates F, Gundu I et al. Comparison of intrathecal hyperbaric and isobaric levobupivacaine in urological surgery. *Minerva Anesthesiol*. 2010;76(1):24-28.
13. Naithani U, Malleshappa K, Madhanmohan, Meena P. Comparison of intrathecal isobaric levobupivacaine with hyperbaric bupivacaine in spinal anesthesia for lower limb orthopedic surgeries. *Int J Health Sci Res* 2015;5:73-84.
14. Verma A, Singariya G, Kamal M, Sethi P, Chouhan DS, Kumari K. Comparison of Different Concentration of Dextrose as an Adjuvant to Levobupivacaine in Lower Limb Surgeries: A Randomised Double-Blinded controlled Trial. *Int J Health Sci Res*. 2018;8(3):11-8.
15. Singh A, Gupta A, Datta PK, Pandey M. Intrathecal levobupivacaine versus bupivacaine for inguinal hernia surgery: a randomized controlled trial. *Korean J Anesthesiol* 2018;71:220-5.
16. Biji KP, Sunil M, Ramadas KT. Comparative Study of Constant Dose Intrathecal Hypobaric Levobupivacaine with Varying Baricities in Lower Limb Surgeries. *Anesth Essays Res* 2017;11:642-6.
17. Cappelleri G, Aldegheri G, Danelli G, Marchetti C, Nuzzi M, Iannandrea G, et al. Spinal anaesthesia with Hyperbaric levobupivacaine and ropivacaine for outpatient knee arthroscopy: a prospective, randomized. Double-blind study. *Anesth Analg*. 2005;101:77-82.
18. Yagan O, Tas N, Kucuk A, Hanci V. A comparison of different densities of levobupivacaine solutions for unilateral spinal anaesthesia. *Braz J Anesthesiol*. 2016;66(2):157-64.
19. Herrera R, De Andres J, Estan L, Olivas FJ, Martínez Mir I, Steinfeldt T. Hemodynamic impact of isobaric levobupivacaine versus hyperbaric bupivacaine for subarachnoid anesthesia in patients aged 65 and older undergoing hip surgery. *BMC Anesthesiol*. 2014 Oct 24;14:97.

