A Comparative Study of Anaesthetic Efficacy of 0.5% Hyperbaric Levobupivacaine Vs 0.5% Hyperbaric Bupivacaine for Intrathecal Anaesthesia in Below Umbilical Surgeries - A Prospective Randomized Study

[1]Dr. Senthil Kumar. B, [2]Dr. Suneeth P. Lazarus, [3]Dr. Dilip Chander

[1] 3rd Year Postgraduate, Department of Anaesthesiology, Sri Manakula Vinayagar Medical College Hospital and Research Centre, PUDUCHERRY, India

[2] Professor and Head, Department of Anaesthesiology, Sri Manakula Vinayagar Medical College Hospital and Research Centre, PUDUCHERRY, India

[3] Professor, Department of Anaesthesiology, Sri Manakula Vinayagar Medical College Hospital and Research Centre, PUDUCHERRY, India

Abstract

Background: Spinal anesthesia is a common technique for below umbilical surgeries, with the choice of local anesthetic playing a crucial role in patient outcomes. This study aimed to compare the anesthetic efficacy and safety of 0.5% hyperbaric Bupivacaine and 0.5% hyperbaric Levobupivacaine for spinal anesthesia in below umbilical surgeries.

Methodology: A prospective randomized study was conducted among patients undergoing elective infraumbilical surgeries under spinal anesthesia at Sri Manakula Vinayagar Medical College Hospital were included. They were randomly assigned to receive either 0.5% hyperbaric Bupivacaine or 0.5% hyperbaric Levobupivacaine intrathecally.

Results: The level of sensory blockade was comparable between the Bupivacaine and Levobupivacaine groups (P = 0.360), indicating similar efficacy in achieving sensory anesthesia. The mean onset time for motor blockade was significantly quicker in the Bupivacaine group (3.46 min) compared to the Levobupivacaine group (9.28 min), with a statistically significant difference (P = 0.001). Similarly, the mean duration of motor blockade was longer in the Bupivacaine group (201.40 min) compared to the Levobupivacaine group (181.28 min), with a significant difference (P = 0.001). There were no significant differences in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, or oxygen saturation between the Bupivacaine and Levobupivacaine groups at various time intervals throughout the study period.

Conclusion: Both 0.5% hyperbaric Bupivacaine and 0.5% hyperbaric Levobupivacaine demonstrated comparable efficacy and safety profiles for spinal anesthesia in below umbilical surgeries.

Keywords: anesthesia, umbilical, Bupivacaine, infraumbilical, demonstrated

INTRODUCTION

Intrathecal anaesthesia is usually used for surgeries below the umbilicus. [1,2]. The selection of an appropriate local anaesthetic agent determines the quality, duration and the incidence of potential adverse effects [3,4]. This study compares two commonly utilized hyperbaric local anaesthetics: Levobupivacaine and Bupivacaine, at a concentration of 0.5%. Levobupivacaine has properties similar to Bupivacaine with fewer cardiotoxic effects owing to its lower affinity for cardiac sodium channels [5].

The comparison of these two agents is needed to study about the efficacy and safety in intrathecal anaesthesia, for surgeries below the umbilicus. While both Levobupivacaine and Bupivacaine have demonstrated efficacy in this context, a paucity of comparative studies exists to delineate potential disparities in their clinical outcomes.

In the perioperative setting, factors like how quickly the sensory and motor blockade starts and how long it lasts, the stability of blood pressure and heart rate, and the likelihood of side effects become extremely important [6,7]. Consequently, a deeper understanding of the pharmacological disparities

between these agents and their clinical ramifications assumes pivotal importance for aspiring healthcare professionals in the fields of anaesthesia [8].

In current medical practice, evaluating 0.5% hyperbaric Levobupivacaine to 0.5% hyperbaric Bupivacaine in intrathecal anaesthesia in procedures below the umbilicus is crucial. By elucidating potential variances in anaesthetic efficacy and safety profiles, this study attempts to help in clinical decision-making processes and advance the overarching goal of optimizing patient outcomes.

MATERIALS AND METHODS

Study setting:

The research took place at Sri Manakula Vinayagar Medical College and Hospital (SMVMCH) within the Department of Anaesthesiology. The study was done on patients who underwent below umbilical surgeries under spinal anaesthesia.

Study design:

The study was conducted as prospective randomized study design, as per Good Clinical Practice (GCP) guidelines laid by World Health Organization (WHO).

Study Period:

The study was conducted over a period of one year and six months after getting clearance from college's Institutional Ethics Committee (IEC) from October 2022 till April 2024.

Study Sample:

All the patients who satisfied the inclusion criteria in the period of this study were equally divided into 2 groups and studied. An initial sample population of 40 in each group, making a total of 80 participants were included in the study.

Considering the onset time of T10 level of the sensorial block between the levobupivacaine and bupivacaine group for transurethral surgery in a study by Erbay H et al of 5+/-2min and 6+/-1 min mean time respectively the sample size for the present study was calculated to be 80 (40 in each group) at 95% confidence interval, 80% power and 1:1 ratio distribution among study groups.

Study Population:

During the study period, patients scheduled for elective surgeries below the umbilicus under spinal anaesthesia at Sri Manakula Vinayagar Medical College Hospital in Pondicherry participated after obtaining consent and receiving clearance from the Institutional Ethics Committee.

Sampling:

Participants were selected as per the inclusion criteria and consecutively enrolled into the study till the desired sample size was achieved.

Randomization:

It was done by block randomization method with block size of 10 with the help of an external person not involved in the study (epidemiology unit of the Community Medicine department). This was done using random allocation software.

Blinding:

Double blinded randomized study was done (patient and the researcher were blinded). The investigator who recorded the data was not aware of the participant's group. The participant did not know to which group he/she was being allotted. Sequence was handed over to the principal investigator in sealed envelope. Decoding was done by the statistician.

Inclusion Criteria --- Patients who underwent elective infraumbilical surgeries under spinal anaesthesia during the study period, Patients of ASA physical status 1 and 2, Patients of either sex, Age >18 years or < 60 years, Patients with height more than 150 cm.

Exclusion Criteria:

Body Mass Index >30, Patients with infection, drug allergy, or other known contraindications present for spinal anaesthesia. Patients who could not lie down/non-co-operative/psychiatric illness, Alcoholics. Pregnant / Lactating women, Patients who failed spinal and transformed into general anaesthesia were excluded from study, Patients who refused to participate in the study, Patients with height less than 150 cm.

Study Procedure:

The study was done at Sri Manakula Vinayagar Medical College and Hospital under the Department of Anaesthesiology after the approval of the institutional ethics and research committee. The study was registered in Clinical Trials Registry India (CTRI registration number:

CTRI/2023/02/0494460). The study design was double-blinded randomized trial. Patients who met the inclusion criteria were briefed about the study's purpose. After receiving informed written consent, they were enrolled in the study. Code number was put on participant proforma sheet, and decoding was done at the end of the study for statistical analysis.

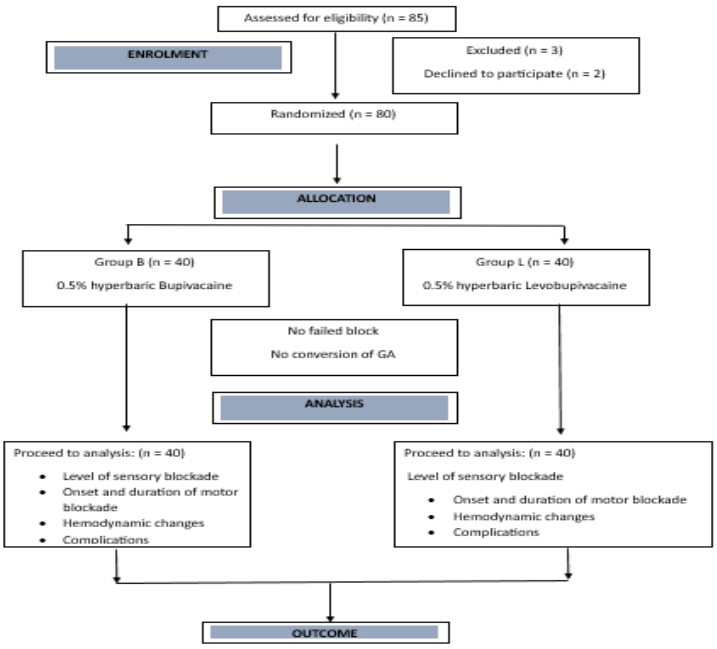
Pre - operative evaluation

Detailed history, Age and weight, Basal heart rate and Blood Pressure, Haemoglobin, Total and differential count, Routine urine examination, Chest X-ray, Type of surgery, Airway assessment.

Patient preparation -- Each patient provided written informed consent before participating. Patients' information was recorded in the proforma. Patients were then assigned to either Group A or Group B through a randomization process. Group A received 0.5% hyperbaric levobupivacaine, while Group B received 0.5% hyperbaric bupivacaine. The drugs were administered by the anaesthesiologist according to the sequence and code provided to each patient. Regular vital signs were monitored and intravenous fluids given. The patient and the researcher were blinded. Under strict aseptic precautions. Intrathecal block via L3-L4 intervertebral space was performed using a 23G Quincke's spinal needle. After a free flow of CSF, 0.5% hyperbaric Bupivacaine/Levobupivacaine 3cc was injected intrathecally at the rate of 0.2m1/second. Then patient was put in a supine position and their vital signs were continuously monitored until the surgery was completed. The sensory and motor blockade were evaluated every 2 minutes until the highest level of block was achieved. Sensory blockade was assessed every 2 minutes post-injection by pin-prick until a stable sensory level was achieved for the next 20 minutes and scored on a three-point scale in the dermatomes (Score 2: sharp pain, score 1: blunt pain, Score 0: no pain). Once sensory blockade began, the highest level of sensory blockade was recorded. Using the pinprick method every 15 minutes, two segment regression time was noted. Motor blockade was evaluated using the Modified Bromage scale. It was assessed every 5 minutes until the maximum motor block was achieved, and then the time it took for normal motor function to return was recorded.

Hemodynamic parameters were recorded till 180 minutes after the drug was administered. These parameters included systolic and diastolic blood pressure, mean arterial pressure (MAP), heart rate, and oxygen saturation. A heart rate below 50 bpm was managed with intravenous atropine 0.6 mg, while hypotension was managed with intravenous ephedrine 6 mg. Adverse reactions such as respiratory depression, bradycardia, hypotension, dizziness, nausea, and vomiting were noted. Any adverse drug reactions were reported to the ethics committee within 24 hours of occurrence.

Figure 6: Consort flowchart for the study.



Sampling technique

Patients were divided into two groups 40 each by block randomization technique. Group A - Patient receiving 0.50% hyperbaric Levobupivacaine. Group B - Patient receiving 0.5% hyperbaric Bupivacaine. Method: Block randomization. Block size: 10, Total number of blocks:8. The randomization sequence was done by individual from the Epidemiology unit. It was then provided to the investigator in sealed opaque envelopes which was opened in sequential order to decide type of block.

Data collection tool -- motor block assessed by Modified Bromage Scale, sensory block assessed by pinprick test, vitals like (pulse, BP, RR) assessed intra operatively, side effects of the bupivacaine and levobupivacaine assessed.

Statistical analysis -- Epi Info software, version 7.2.1.0, was used for data input. The statistical analysis was performed with version 24.0 of SPSS. The mean and standard deviation were used to characterize the study variables. When comparing quantitative variables, the two-tailed independent sample t-test was employed; when comparing qualitative variables, the Chi-squared test was utilized. P value of <0.05 was considered significant.

Description of drugs used in the two groups:

Group A received 0.5% Hyperbaric Levobupivacaine & Group B received 0.5% Hyperbaric Bupivacaine.

RESULTS

The data was collected from a total of 80 study participants, 40 participants each in the Bupivacaine (B) and Levobupivacaine (L) groups respectively.

Table 1: Comparison of demographic profile between two groups.

Variable	Group B (n=40)	GROUP L (n=40)	P-value
Age in years	48.05	40.45	0.003
Height in cm	160.03	161.25	0.576
Weight in Kg	64.40	63.39	0.848
ASA 1	5	22	0.001
ASA 2	35	18	

Gender distribution was identical in both groups, with each group consisting of 50% males and 50% females (χ^2 = 0.000, p = 1.000). Chi-square test revealed notable disparity in the ASA classifications between the B and L groups. (P = 0.001)

Table 2: Comparison of results of spinal anaesthesia between two groups.

Variable		Group B (n=40)	GROUP L (n=40)	P-value
Onset of motor blockade in minutes		3.46	9.28	0.001*
Duration of motor blockade in minutes		201.40	181.28	0.001*
Level of sensory blockade	T6	22	18	0.360
	T8	17	22	
	T10	1	0	
Two segment regression time in minutes		105.68	102.62	0.253

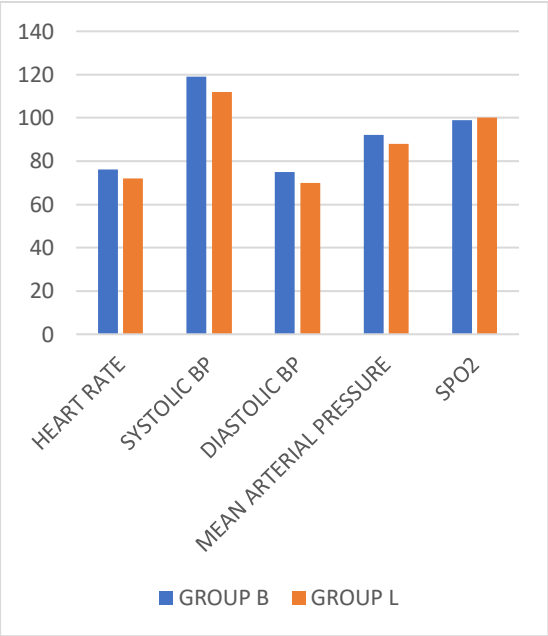
Level of sensory blockade was comparable between the Bupivacaine and Levobupivacaine groups (P = 0.360). The mean onset time for motor blockade were significantly quicker in the Bupivacaine group (3.46 min) when compared to the Levobupivacaine group (9.28 min) with a P value of 0.001. Similarly, the mean duration of motor blockade was longer in the Bupivacaine group (201.40 min) when compared to the Levobupivacaine group (181.28 min) with a P value of 0.001.

Table 3 Comparison of complication between two groups.

Complications	Group B (n=40)	Group L (n=40)	P value
Bradycardia	0	0	1.000
Hypotension	8	1	0.013
Respiratory depression	0	0	1.000
Nausea and vomiting	0	1	0.314

Incidence of complications such as bradycardia, respiratory depression, nausea and vomiting were similar between the two groups, with no statistically significant differences observed (P > 0.05). However, hypotension was found to be more in the bupivacaine group (P = 0.013)

Figure 1 comparison of haemodynamic parameters between two groups.



No significant differences in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, or oxygen saturation between the Bupivacaine and Levobupivacaine groups at various time intervals throughout the study period.

DISCUSSION

The study was conducted to compare the anaesthetic efficacy of 0.5% hyperbaric Levobupivacaine with 0.5% hyperbaric Bupivacaine for intrathecal anaesthesia in below umbilical surgeries. A prospective study was designed involving 80 participants, evenly distributed into two groups: the Bupivacaine (B) group and the Levobupivacaine (L) group, each comprising 40 patients. The objective was to evaluate the onset, duration, and quality of sensory and motor blockade, as well as hemodynamic effects and complications associated with the administration of these two local anaesthetics.

The significance of this study lies in the clinical decision-making process regarding the selection of the most suitable local anaesthetic agent for spinal anaesthesia in surgeries below the umbilicus. Bupivacaine and levobupivacaine are both widely used for intrathecal anaesthesia due to their long duration of action and favourable safety profiles. However, the comparative efficacy and safety of these agents in this specific surgical population have not been thoroughly investigated.

Demographic characteristics:

The comparison of demographic characteristics between the two study groups, namely age, height, weight, and gender distribution, is crucial in understanding the baseline characteristics of the study population and ensuring the comparability of the groups. In our investigation, we observed notable differences in age distribution between the Bupivacaine (B) (mean age = 48.05 years) and Levobupivacaine (L) (mean age = 40.45 years) groups, with the mean age being significantly higher in the Bupivacaine group. Advancing age is associated with physiological changes that may affect drug metabolism and hemodynamic stability.Previous studies [21, 24] have reported similar findings, highlighting the importance of considering age as a potential confounding factor in comparative studies of anaesthetic agents.

Furthermore, our analysis of gender distribution revealed no significant differences between the Bupivacaine and Levobupivacaine groups, with an equal distribution of males and females in both groups. While gender-based disparities in anaesthesia outcomes have been reported in some studies [22, 27], our findings suggest that gender may not be a significant confounding factor in the comparison of bupivacaine and levobupivacaine for spinal anaesthesia in below umbilical surgeries.

Comparative studies investigating the demographic characteristics of patients undergoing spinal anaesthesia with bupivacaine and levobupivacaine have yielded inconsistent results. Some studies [25, 29] have reported similar age distributions between the two groups, while others [21, 24] have noted differences in age and gender distribution similar to our findings.

ASA category:

In our study, we observed significant differences in ASA classification between the Bupivacaine (B) and Levobupivacaine (L) groups, with a higher proportion of patients classified as ASA category 1

in the Levobupivacaine group (81.5%) compared to the Bupivacaine group (34%). This discrepancy in ASA classification may reflect variations in the baseline health status and comorbidity burden among patients [41, 42].

Onset and duration of motor blockade:

We found significant differences in these parameters when comparing the onset and duration of motor blockage between the levobupivacaine (L) and bupivacaine (B) groups in our investigation. With a p-value of 0.001, the bupivacaine group saw a substantially faster start of motor blockage (3.46 ± 1.23 minutes) than the levobupivacaine group (9.28 ± 3.69 minutes). Similarly, the duration of motor blockade was significantly longer in the bupivacaine group (201.40 ± 14.22 minutes) compared to the levobupivacaine group (181.28 ± 21.14 minutes) with a p-value of 0.001.

These findings are consistent with previous research [24, 25] indicating that bupivacaine typically results in a faster onset of motor blockade, but longer duration compared to levobupivacaine. The faster onset of motor blockade with bupivacaine may be attributed to its higher lipid solubility and faster onset of action compared to levobupivacaine. On the other hand, the shorter duration of motor blockade with levobupivacaine may be due to its shorter elimination half-life and lower degree of protein binding, leading to more rapid clearance from the central nervous system [43].

The mean onset time for motor blockade were significantly quicker in the Bupivacaine group (3.46 min) when compared to the Levobupivacaine group (9.28 min) with a P value of 0.001. Similarly, the mean duration of motor blockade was longer in the Bupivacaine group (201.40 min) when compared to the Levobupivacaine group (181.28 min) with a P value of 0.001. [44,45]

Level of sensory blockade:

In our investigation of the level of sensory blockade between bupivacaine (B) and levobupivacaine (L) groups, we found comparable outcomes with no significant differences observed ($p = 0.360$). The distribution of sensory blockade was similar between the two groups, with the majority of participants experiencing blockade at the T6 and T8 dermatomal levels. Notably, there was a single participant in the bupivacaine group who achieved sensory blockade up to the T10 level, while none in the levobupivacaine group reached this extent.

Comparing our findings with previous research [27, 31], which also examined the level of sensory blockade between bupivacaine and levobupivacaine groups, our results align with the existing literature. Consistent trends suggest that both local anaesthetics offer comparable levels of sensory blockade in below umbilical surgeries. This parity in sensory blockade distribution implies that both bupivacaine and levobupivacaine are effective choices for achieving adequate surgical anaesthesia in this patient population [45].

Two segment regression time:

Our investigation into the two-segment regression time, comparing bupivacaine (B) and levobupivacaine (L) groups, revealed no statistically significant difference in mean regression times ($p = 0.253$). The mean regression time for the bupivacaine group was 105.68 minutes, while for the levobupivacaine group, it was 102.62 minutes. Although the difference was not statistically significant, there was a trend towards a slightly longer regression time in the bupivacaine group.

Comparing these findings with prior studies [23, 24], we observed consistent trends indicating similar regression times between bupivacaine and levobupivacaine groups [46].

Hemodynamic effects:

On analysing heart rate, we observed no significant difference between the bupivacaine (B) and levobupivacaine (L) groups at any time point ($p > 0.05$). These findings are consistent with previous studies [26, 29] that also reported comparable heart rates between patients receiving either bupivacaine or levobupivacaine for spinal anaesthesia. While our study found no significant differences in heart rate between patients receiving bupivacaine or levobupivacaine [47].

Regarding SBP, our findings revealed a statistically significant difference at different time intervals between the two groups. SBP in the bupivacaine group was considerably lower at 6 minutes than in the levobupivacaine group ($p = 0.008$). This result contrasts with earlier studies [32], which found no appreciable variation in SBP between the two groups receiving local anaesthetic. Likewise, notable variations were noted for DBP at various

intervals. Notably, at 6 minutes, DBP was significantly lower in the bupivacaine group compared to the levobupivacaine group ($p = 0.029$). These findings deviate from those of a previous study [34], which found no significant disparity in DBP between the two groups. Changes in SBP and DBP reflect the vascular response to anaesthesia-induced sympathetic blockade. A decrease in SBP and DBP, as observed in the bupivacaine group at specific time points, may indicate hypotension, reducing myocardial oxygen delivery and potentially leading to myocardial ischemia or other cardiovascular complications [48, 49].

Regarding MAP, our study revealed no statistically significant difference between the bupivacaine and levobupivacaine groups at any time point ($p > 0.05$). These results are in line with existing literature [28, 35], which consistently reported similar MAP values between patients receiving bupivacaine or levobupivacaine for spinal anaesthesia. Although our study did not find significant differences in MAP between the two groups, maintaining MAP within normal range is critical for preserving organ function and preventing perioperative complications, such as acute kidney injury or cerebral hypoperfusion [50].

Lastly, analysing SpO2, we found no significant difference between the two groups at any time interval ($p > 0.05$). This finding aligns with previous studies [27, 30]. Close monitoring of SpO2 remains essential throughout the intraoperative period to promptly detect and address any respiratory insufficiency or airway obstruction. Continuous pulse oximetry monitoring minimizing the risk of hypoxemia-related complications [51, 52].

Postoperative complications:

In our study hypotension occurred more frequently in the bupivacaine group (88.9% vs. 11.1%, $P = 0.013$). This discrepancy aligns with previous research [29] that demonstrated a higher incidence of hypotension with bupivacaine due to its greater cardiovascular depressant effects compared to levobupivacaine. The vasodilatory properties of bupivacaine can lead to a more pronounced decrease in systemic vascular resistance, resulting in hypotension in vulnerable groups [53, 54].

In contrast, no cases of bradycardia were observed in either group in our study, indicating a similar cardiovascular stability profile between bupivacaine and levobupivacaine. This finding is consistent with the results of Goyal A et al. [28].

Respiratory depression, another potential complication of intrathecal anaesthesia, was not observed in either group in our study, corroborating the safety of both bupivacaine and levobupivacaine in terms of respiratory function. This finding is consistent with the results of several previous studies [22, 25, 27] that reported minimal respiratory depression.

The occurrence of vomiting was comparable between two groups with no significant difference observed. This finding contrasts with the results of Bremerich DH et al. [32], which reported a higher incidence of nausea and vomiting with bupivacaine compared to levobupivacaine.

Conclusion:

Both 0.5% hyperbaric Bupivacaine and 0.5% hyperbaric Levobupivacaine demonstrated comparable efficacy and safety profiles for spinal anaesthesia in below umbilical surgeries.

Limitations of the study:

1. Single-Centre Study: The study was conducted at a single center, which may limit the generalizability of the findings to other healthcare settings.
2. Short Follow-up Period: The study's follow-up period was relatively short, focusing primarily on intraoperative and immediate postoperative outcomes.
3. Patient Population: The study may have lacked diversity in its patient population, potentially limiting the generalizability of the findings to a broader demographic group.
4. Exclusion of Certain Patient Groups: The study may have excluded patients with specific medical conditions or anatomical considerations that could affect the response to spinal anesthesia with Bupivacaine or Levobupivacaine.
5. Confounding Variables: Despite efforts to control for confounding variables through randomization and standardized protocols, residual confounding may still exist.

References

1. 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 Oct;109(4):1331-4.
2. Guo J, Lv N, Su Y, Liu Y, Zhang J, Yang D. Effects of intrathecal anesthesia with different concentrations and doses on spinal cord, nerve roots and cerebrospinal fluid in dogs. Int J Clin Exp Med. 2014 Dec 15;7(12):5376-84.
3. Uppal V, Shanthanna H, Prabhakar C, McKeen DM. Intrathecal hyperbaric versus isobaric bupivacaine for adult non-caesarean-section surgery: systematic review protocol. BMJ Open. 2016 May 18;6(5):e010885.
4. Siddaiah J, Pujari VS, Madalu AS, Bevinaguddaiah Y, Parate LH. A comparative study on the effect of addition of intrathecal buprenorphine to 2-chloroprocaine spinal anesthesia in short duration surgeries. J Anaesthesiol Clin Pharmacol. 2019 Oct-Dec;35(4):533-539.
5. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review. J Anaesthesiol Clin Pharmacol. 2013 Oct;29(4):530-9.
6. Urbanek B, Kapral S. Levobupivacaine for regional anesthesia. A systematic review. Anaesthesist. 2006 Mar;55(3):296-313.
7. Besha A, Zemedkun A, Tadesse M, Hailu S, Mossie A, Shiferaw A, Angasa D, Adamu Y. Effects of Hyperbaric and Isobaric Bupivacaine on Hemodynamic Profiles and Block Characteristics Among Parturients Undergoing Elective Cesarean Section Under Spinal Anesthesia: A Randomized Controlled Trial. J Pain Res. 2023 Oct 20;16:3545-3558.
8. Abebe MM, Arefayne NR, Temesgen MM, Admass BA. Incidence and predictive factors associated with hemodynamic instability among adult surgical patients in the post-anesthesia care unit, 2021: A prospective follow up study. Ann Med Surg (Lond). 2022 Jan 29;74:103321.
9. Bican O, Minagar A, Pruitt AA. The spinal cord: a review of functional neuroanatomy. Neurol Clin. 2013 Feb;31(1):1-18.
10. Frostell A, Hakim R, Thelin EP, Mattsson P, Svensson M. A Review of the Segmental Diameter of the Healthy Human Spinal Cord. Front Neurol. 2016;7:238.
11. Diaz E, Morales H. Spinal Cord Anatomy and Clinical Syndromes. Semin Ultrasound CT MR. 2016 Oct;37(5):360-71.
12. Gilchrist RV, Frey ME, Nadler SF. Muscular control of the lumbar spine. Pain Physician. 2003 Jul;6(3):361-8.
13. Hartmann B, Junger A, Klasen J, Benson M, Jost A, Banzhaf A, Hempelmann G. The incidence and risk factors for hypotension after spinal anesthesia induction: an analysis with automated data collection. Anesth Analg. 2002 Jun;94(6):1521-9.
14. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992 Jun;76(6):906-16.
15. Doelakeh ES, Chandak A. Risk Factors in Administering Spinal Anesthesia: A Comprehensive Review. Cureus. 2023 Dec 4;15(12):e49886.
16. Gao L, Yang Z, Zeng S, Li J, Wang N, Wang F. The potencies and neurotoxicity of intrathecal levobupivacaine in a rat spinal model: Effects of concentration. Pharmacol Res Perspect. 2023 Aug;11(4):e01116.
17. Halpern S, Preston R. Postdural puncture headache and spinal needle design. Metaanalyses. Anesthesiology. 1994 Dec;81(6):1376-83.
18. Chattopadhyay I, Jha AK, Banerjee SS, Basu S. Post-procedure adhesive arachnoiditis following obstetric spinal anaesthesia. Indian J Anaesth. 2016 May;60(5):372-4.
19. Li J, Duan R, Zhang Y, Zhao X, Cheng Y, Chen Y, Yuan J, Li H, Zhang J, Chu L, Xia D, Zhao S. Beta-adrenergic activation induces cardiac collapse by aggravating cardiomyocyte contractile dysfunction in bupivacaine intoxication. PLoS One. 2018;13(10):e0203602.
20. Iskander A, Gan TJ. Novel analgesics in ambulatory surgical patients. Curr Opin Anaesthesiol. 2018 Dec;31(6):685-692.
21. Piacherski V, Muzyka L. Comparison of the efficacy of 0.5% isobaric bupivacaine, 0.5% levobupivacaine, and 0.5% hyperbaric bupivacaine for spinal anesthesia in lower limb surgeries. Sci Rep. 2023 Feb 15;13(1):2736.
22. Sahin SH, Inal M, Alagol A, Colak A, Arar C, Basmergen T, Gunday I, Turan FN. Effects of bupivacaine versus levobupivacaine on pulmonary function in patients with chronic obstructive pulmonary disease undergoing urologic surgery: a randomized, double-blind,

controlled trial. Curr Ther Res Clin Exp. 2011 Aug;72(4):164-72.
23. Vives R, Fernandez-Galinski D, Gordo F, Izquierdo A, Oliva JC, Colilles C, Pontes C. Effects of bupivacaine or levobupivacaine on cerebral oxygenation during spinal anesthesia in elderly patients undergoing orthopedic surgery for hip fracture: a randomized controlled trial. BMC Anesthesiol. 2019 Jan 31;19(1):17.
24. Sundarathiti P, Sangdee N, Sangasilpa I, Prayoonhong W, Papoun S. Comparison of intrathecal bupivacaine, levobupivacaine for cesarean section. J Med Assoc Thai. 2014 Jul;97(7):710-6.
25. Luck JF, Fettes PD, Wildsmith JA. Spinal anaesthesia for elective surgery: a comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine. Br J Anaesth. 2008 Nov;101(5):705-10.
26. Debbarma B, Yumnam AS, Laithangbam PKS, Singh TH, Singh TR, Singh NR. A comparative study of hyperbaric bupivacaine (0.5%) with hyperbaric levobupivacaine for spinal anesthesia in cesarean section: a randomized, controlled trial. JMS - Journal of Medical Society. 2017;31(1):32-36.
27. Goyal A, Singi Y, Mallya P, Bhat G, P S. A Comparison Between Intrathecal Levobupivacaine and Bupivacaine for Quality and Safety During Infraumbilical Surgeries. Cureus. 2022 Oct 22;14(10):e30590.
28. Goyal A, Shankaranarayan P, Ganapathi P. A randomized clinical study comparing spinal anesthesia with isobaric levobupivacaine with fentanyl and hyperbaric bupivacaine with fentanyl in elective cesarean sections. Anesth Essays Res. 2015 Jan-Apr;9(1):57-62.
29. Oraon P, Hembrom B, Kumar M, Ram B, Lakra L. Comparative Study between Intrathecal 0.5% Isobaric Levobupivacaine, 0.5% Isobaric Ropivacaine, and 0.5% Hyperbaric Bupivacaine in Elective Lower Segment Cesarean Section: A Randomized Clinical Study. Anesth Essays Res. 2022 Apr-Jun;16(2):238-243.
30. Singh A, Gupta A, Datta PK, Pandey M. Intrathecal levobupivacaine versus bupivacaine for inguinal hernia surgery: a randomized controlled trial. Korean J Anesthesiol. 2018 Jun;71(3):220-225.
31. Chen CK, Lau FC, Lee WG, Phui VE. Levobupivacaine vs racemic bupivacaine in spinal anesthesia for sequential bilateral total knee arthroplasty: a retrospective cohort study. J Clin Anesth. 2016 Sep;33:75-80.
32. Bremerich DH, Fetsch N, Zwissler BC, Meininger D, Gogarten W, Byhahn C. Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for Caesarean section. Curr Med Res Opin. 2007 Dec;23(12):3047-54.
33. Sethi D. Randomised Control Trial Comparing Plain Levobupivacaine and Ropivacaine with Hyperbaric Bupivacaine in Caesarean Deliveries. Turk J Anaesthesiol Reanim. 2019 Dec;47(6):471-479.
34. Deepa T, Chandran D. Effect of addition of intrathecal magnesium sulphate to 0.5% hyperbaric bupivacaine and 0.5% isobaric levobupivacaine on duration of analgesia in parturients undergoing elective caesarean section: A prospective randomised study. J Anaesthesiol Clin Pharmacol. 2021 Oct-Dec;37(4):633-638.
35. Turkmen A, Moralar DG, Ali A, Altan A. Comparison of the anesthetic effects of intrathecal levobupivacaine + fentanyl and bupivacaine + fentanyl during caesarean section. Middle East J Anaesthesiol. 2012 Feb;21(4):577-82.
36. Pehlivan VF, Akçay M, İkeda ÖC, Göğüş N. Comparison Between the Effects of Bupivacaine and Levobupivacaine for Spinal Anesthesia on QT Dispersion. Cardiovasc Hematol Disord Drug Targets. 2021;21(1):66-72.
37. Hakan Erbay R, Ermumcu O, Hanci V, Atalay H. A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: a randomized controlled trial. Minerva Anestesiol. 2010 Dec;76(12):992-1001.
38. del-Rio-Vellosillo M, Garcia-Medina JJ, Abengochea-Cotaina A, Pinazo-Duran MD, Barbera-Alacreu M. Spinal anesthesia for knee arthroscopy using isobaric bupivacaine and levobupivacaine: anesthetic and neuroophthalmological assessment. Biomed Res Int. 2014;2014:349034.
39. Şahin AS, Türker G, Bekar A, Bilgin H, Korfalı G. A comparison of spinal anesthesia characteristics following intrathecal bupivacaine or levobupivacaine in lumbar disc surgery. Eur Spine J. 2014 Mar;23(3):695-700.

40. Ture P, Ramaswamy AH, Shaikh SI, Alur JB, Ture AV. Comparative evaluation of anaesthetic efficacy and haemodynamic effects of a combination of isobaric bupivacaine with buprenorphine vs. isobaric levobupivacaine with buprenorphine for spinal anaesthesia - A double blinded randomised clinical trial. Indian J Anaesth. 2019 Jan;63(1):49-54.
41. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs. 2000 Mar;59(3):551-79.
42. De Cassai A, Boscolo A, Tonetti T, Ban I, Ori C. Assignment of ASA-physical status relates to anesthesiologists' experience: a survey-based national-study. Korean J Anesthesiol. 2019 Feb;72(1):53-59.
43. Bockholt R, Mirus M. Principles of the pharmacology of local anesthetics. Anaesthesiologie. 2024 Mar;73(3):204-220.
44. Mahan MC, Jildeh TR, Tenbrunsel T, Adelman BT, Davis JJ. Time of return of neurologic function after spinal anesthesia for total knee arthroplasty: mepivacaine vs bupivacaine in a randomized controlled trial. Arthroplast Today. 2019 May 3;5(2):226-233.
45. Singh A, Gupta A, Datta PK, Pandey M. Intrathecal levobupivacaine versus bupivacaine for inguinal hernia surgery: a randomized controlled trial. Korean J Anesthesiol. 2018 Jun;71(3):220-225.
46. Sia AT, Tan KH, Sng BL, Lim Y, Chan ES, Siddiqui FJ. Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. Cochrane Database Syst Rev. 2013 May 31;(5):CD005143.
47. Guinet P, Estebe JP, Ratajczak-Enselme M, Bansard JY, Chevanne F, Bec D, Lecorre P, Wodey E, Ecoffey C. Electrocardiographic and hemodynamic effects of intravenous infusion of bupivacaine, ropivacaine, levobupivacaine, and lidocaine in anesthetized ewes. Reg Anesth Pain Med. 2009 Jan-Feb;34(1):17-23.
48. Herrera R, De Andrés J, Estañ 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.
49. Vives R, Fernandez-Galinski D, Gordo F, Izquierdo A, Oliva JC, Colilles C, Pontes C. Effects of bupivacaine or levobupivacaine on cerebral oxygenation during spinal anesthesia in elderly patients undergoing orthopedic surgery for hip fracture: a randomized controlled trial. BMC Anesthesiol. 2019 Jan 31;19(1):17.
50. Uppal V, Retter S, Shanthanna H, Prabhakar C, McKeen DM. Hyperbaric Versus Isobaric Bupivacaine for Spinal Anesthesia: Systematic Review and Meta-analysis for Adult Patients Undergoing Noncesarean Delivery Surgery. Anesth Analg. 2017 Nov;125(5):1627-1637.
51. Pedersen T, Nicholson A, Hovhannisyan K, Møller AM, Smith AF, Lewis SR. Pulse oximetry for perioperative monitoring. Cochrane Database Syst Rev. 2014 Mar 17;2014(3):CD002013.
52. Nardini S, Corbanese U, Visconti A, Mule JD, Sanguinetti CM, De Benedetto F. Improving the management of patients with chronic cardiac and respiratory diseases by extending pulse-oximeter uses: the dynamic pulse-oximetry. Multidiscip Respir Med. 2023 Dec 20;18(1):922.
53. Nakasuji M, Suh SH, Nomura M, Nakamura M, Imanaka N, Tanaka M, Nakasuji K. Hypotension from spinal anesthesia in patients aged greater than 80 years is due to a decrease in systemic vascular resistance. J Clin Anesth. 2012 May;24(3):201-6.
54. Hofhuizen C, Lemson J, Snoeck M, Scheffer GJ. Spinal anesthesia-induced hypotension is caused by a decrease in stroke volume in elderly patients. Local Reg Anesth. 2019 Mar 4;12:19-26.