



COMPARISON OF OUTCOME OF 0.5% HYPERBARIC BUPIVACAINE WITH 0.5% HYPERBARIC ROPIVACAINE IN SPINAL ANAESTHESIA FOR PERIANAL SURGERIES.

Hira Shujaat¹, Mehreen Khan², Ravi Kumar³, Muhammad Waseem Abdul Razzak⁴, Vijai Kumar⁵, Zamir Ahmad⁶.

Abstract

Introduction: The field of anaesthesiology has undergone significant advancements in recent years, resulting in improved patient outcomes and reduced hospitalization durations. This is primarily due to the availability of anaesthetic agents that block sensations locally or regionally for shorter durations. **Objective:** To compare the outcome of 0.5% hyperbaric Ropivacaine with 0.5% hyperbaric Bupivacaine in spinal anaesthesia for perianal surgeries. **Design:** Randomized controlled trial. **Setting:** Anaesthesiology Department, Surgical Intensive Care Unit And Pain Management, Jinnah Post graduate Medical Centre (JPMC), Karachi. **Duration:** Six months (From 7 April 2016 to 7 October 2016). **Methods:** 126 Perianal surgery patients were approached for consent for study. Two groups viz; A & B were made, and group allocation of consecutive patients were made through using opaque envelopes containing strip of either group. Group A patients received three milliliter of Ropivacaine (5 mg/ml) with glucose 83 mg/ml. Whereas, Group B received three milliliter of hyperbaric Bupivacaine (5 mg/ml) with glucose 80 mg/ml. Moreover, Oral temazepam 10–20 mg was administered to patients before to surgery to reduce anxiety. **Results:** The duration of sensory block was statistically less in the Ropivacaine group (153.8±9.3min) as compared to Bupivacaine group (190.2±8.3min) with P-value 0.0001. In addition, the ropivacaine group's mean time in motor block was less than that of the bupivacaine group (120.89±12.122 min vs 189.33±11.947min; P = 0.0001). **Conclusion:** According to the results of the current investigation, bupivacaine applied intrathecally causes sensory block to begin more quickly and last longer than ropivacaine.

Keywords: Hyperbaric bupivacaine, ropivacaine, spinal anaesthesia

1. Consultant Anaesthesia, Fatimiyah Hospital, Karachi, Pakistan
2. Anaesthesia Consultant, Memon Medical Institute Hospital, Karachi, Pakistan
3. Registrar, Department Of Anaesthesiology Critical Care And Pain Management Al Adan Hospital Moh Kuwait.
4. Anaesthesia Specialist, Memon Medical Institute Hospital, Karachi, Pakistan.
5. Assistant Professor, Department Of Anaesthesia, Sindh Institute Of Urology & Transplantation, Karachi, Pakistan.
6. Associate Professor, Department Of Anaesthesiology, Sindh Institute Of Urology And Transplantation, Karachi, Pakistan,

Corresponding Author: Dr. Ravi Kumar Registrar, Department of Anaesthesiology Critical care and Pain management Al Adan hospital MOH Kuwait. Email: 36ravimoolchandani@gmail.com

How to cite this article: Shujaat H¹, Khan M², Kumar R³, Razzak MWA⁴, Kumar V⁵, Ahmad Z⁶. **COMPARISON OF OUTCOME OF 0.5% HYPERBARIC BUPIVACAINE WITH 0.5% HYPERBARIC ROPIVACAINE IN SPINAL ANAESTHESIA FOR PERIANAL SURGERIES.** *JPUMHS*; 2023; 13:01, 99-109 <http://doi.org/10.46536/jpumhs/2023/13.01.392>

Received February 26, 2023, Accepted On 25 March 2023, Published On 31 March 2023.



© 2021 This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), **Attribution-Share Alike CC BY-SA**. This license lets others remix, adapt, and build upon your work even for commercial purposes, as long as they credit you and license their new creations under the identical terms

INTRODUCTION

Spinal anaesthesia is a commonly used regional anaesthesia technique for lower abdominal, pelvic, and lower extremity surgeries^{1,2}. It entails injecting a local anaesthetic into the cerebrospinal fluid (CSF), which causes the lower body's feeling and motor function to be lost⁽²⁾. Hyperbaric local anaesthetics are preferred for spinal anaesthesia due to their rapid onset and predictable duration of action³. Hyperbaric solutions have a higher specific gravity than cerebrospinal fluid, resulting in the drug settling in the dependent area of the spinal cord, providing more reliable anaesthesia^{2,4}. Among hyperbaric local anaesthetics, bupivacaine and ropivacaine are commonly used drugs for spinal anaesthesia⁵. A long-acting amide local anaesthetic having a gradual start and protracted duration of action is bupivacaine³. It provides reliable sensory and motor block but has a higher incidence of cardiovascular toxicity and neurotoxicity⁽⁶⁾. It has a better safety profile, with a lower incidence of motor blockade and cardiovascular toxicity and a lower risk of neurotoxicity⁷. Bupivacaine and ropivacaine's clinical effectiveness and safety in spinal anaesthesia have been compared in several research^{3,8}. However, the results have been conflicting, with some studies showing

similar outcomes between the two drugs while others reporting better outcomes with ropivacaine. Therefore, there is a need for further research to determine the optimal local anaesthetic agent for spinal anaesthesia⁸. In this study, the effectiveness of 0.5% hyperbaric bupivacaine and 0.5% hyperbaric ropivacaine during spinal anaesthesia will be compared^(1, 8). The primary objective of the study is to evaluate the onset and duration of sensory and motor blockade, the quality of anaesthesia, and hemodynamic stability.

METHODOLOGY

This randomized controlled trial study was conducted in Department of Anaesthesiology, Surgical Intensive Care Unit and Pain Management, Jinnah Post Graduate Medical Center (JPMC), Karachi. The study was carried out in duration of six (06) months (from April to October 2016) after taking the approval of synopsis. A total of 126 patients were recruited and categorized in two groups (63 in each group).
 P1 = 155 ± 60 (Mean ±SD) time duration of sensory block (Ropivacaine)
 P2 = 190.5 ± 80 (Mean ±SD) time duration of sensory block (Bupivacaine)
 Power of the study = 80%.

Two sided confidence level = 95%

A non-probability consecutive sampling technique was used for patients recruitment. The patient of age between 18 - 60 years irrespective of gender, admitted patients for perianal surgery under American Society of Anesthesiologists (ASA) class I & II, and willingness to participate in study were included in the study. A patients with hypertensive or hypotensive history, patients with abnormal coagulation profiles (detected through PT, APTT test which are routinely done as part of patient preparation), and American Society of Anesthesiologists class III & IV group patients, severe cardiopulmonary disease, diabetes mellitus detected from the history and examination, and patient on steroid medication, or have taken steroids in the last three months detected from the history were excluded from the study. A data were collected after getting approval of synopsis from Research Evaluation Unit of CPSP, Karachi followed by permission from the ethical review committee of JPMC. Patients admitted for perianal surgery were approached for consent for study once found suitable as per ASA criteria. After understanding the procedures; only those who provide valid written consent were included in the study. Two groups; A & B were made and group allocation of consecutive patients were made thorough using opaque envelopes containing strip of either group. Patients were asked to pick any one of the opaque envelopes thus randomly choosing either A or B group. Participants in group A were given 3 ml of hyperbaric bupivacaine 5 mg/ml (with glucose 80 mg/ml), while those in group B received 3 ml of ropivacaine 5 mg/ml (with glucose 83 mg/ml). To relieve anxiety, oral temazepam 10-20 mg were given preoperatively. Assessment of the sensory blockade was done every minute. After determining the latency time, the assessment were done

every 5 minutes until the 20th minute. Assessment of the motor blockade of the lower limbs were done at 10, 30 and 60 minutes, at the end of the surgical procedure and finally at 120 minutes. The durations of the sensory and motor blockage were noted on proforma. Continuous cardiovascular monitoring with ECG, non-invasive arterial pressure and pulseoximetry were done every three minutes in the first 15 minutes, and every five minutes until the end of the surgical procedure. Hypotension were treated with phenylephrine (50 mcg). The data of name, age, gender, weight, height, address and outcome were noted on proforma. Data were entered and analyzed by using statistical package for social sciences version 19 (SPSS 19). Results were described as mean \pm standard deviation for quantitative variables like age and BMI, duration of sensory and motor blockages in both groups. Frequency and percentage were computed for qualitative variables like gender & residence. Duration of motor and sensory blockade of both anaesthetic agents were compared by using student's t-test (two sample independent) with p value ≤ 0.05 considered as significant. Confounders of outcome variable by age, gender, residence and BMI were evaluated by stratification followed by t-test with p value ≤ 0.05 considered as significant.

RESULTS

A total of 126 patients fulfilling selection criteria for perianal surgery were included in the study. Two groups; A & B were made and group allocation of consecutive patients were made thorough using opaque envelopes containing strip of either group. Patients were asked to pick any one of the opaque envelopes thus randomly choosing either A or B group. Whereas group B patients got 3 ml of hyperbaric bupivacaine 5 mg/ml (with glucose 80 mg/ml), group A

patients received three (03) ml of ropivacaine 5 mg/ml (with glucose 83 mg/ml). To relieve anxiety, oral temazepam 10-20 mg were given preoperatively.

Patients who included in the study have age range 18-60 mean age of patients on Bupivacaine Group was 40.83 with standard deviation 11.47, mean age of patients in ropivacaine Group was 39.56 with standard deviation 10.64, body mass index of Bupivacaine Group were showed mean 27.6 and SD 5.61 body mass index of ropivacaine Group were showed mean 224.17 and SD 7.21 (Table 1).

A study outcomes duration of motor blockages and sensory blockages were presented as mean and standard deviation in Ropivacaine group mean and SD were 120.9±12.1 and in bupivacaine group 189.2±11.9 of duration of motor blockages. Duration of sensory blockages showed mean and standard deviation in bupivacaine group 190.2±8.3 while ropivacaine group 153.8±9.3 (Table 2).

Distributions of gender and residence status of the patients were presented as frequency and percentages qualitative study variables were presented group-wise as well as overall. In Bupivacaine group there were 25(39.7%) study participants were female and 38(60.3%) were male. While in

Ropivacaine group 31 (49.2%) study participants were female and 32(50.8%) were male. Proportion of male and female participants was closely similar. In Bupivacaine group there were 29 (46.03%) study participants were belonged to urban area and remaining were from rural area While in Ropivacaine group 40 (63.49%) study participants were belonged to urban area and only 23(36.51%) were from rural area (Table 3).

Comparison of duration of motor blockages and sensory blockages has been done between both of the study groups mean and SD of both outcomes in Bupivacaine group and ropivacaine group were calculated Result were showed significance difference between both groups (p-value=0.0001) and(p-value=0.0001) respectively. Result obtained by using independent t- test as it was mentioned in the data analysis (Table 4 and 5).

Stratification of duration of motor blockages and sensory blockages between both study groups has been done with regards to age groups, gender, residential status, and BMI. All the results were showing significant differences. which means these factors are affected on the duration of motor and sensory blockages (Table 6-13).

Table 1: Patients categorized based on Ropivacaine and Bupivacaine groups

Drug	Mean±SD	Age	BMI
Ropivacaine	N	63	63
	Mean	39.56	27.6
	Std. Deviation	10.64	5.61
Bupivacaine	N	63	63
	Mean	40.83	24.17
	Std. Deviation	11.47	7.21

Table 2: Outcome of patients in Ropivacaine and Bupivacaine groups

Groups	Mean±SD	Duration of Motor Blockage	Duration of Sensory Blockage
Ropivacaine	N	63	63
	Mean	120.89	153.81
	Std. Deviation	12.122	9.312
Bupivacaine	N	63	63
	Mean	189.22	190.25
	Std. Deviation	11.947	8.312

Table 3: Distribution of gender and residence in Ropivacaine and Bupivacaine groups

Groups	Parameters	Ropivacaine	Bupivacaine
Gender	Female	31(49.2%)	25(39.7%)
	Male	32(50.8%)	38(60.3%)
	Total	63(100%)	63(100%)
Residence	Urban	23(36.51%)	29(46.03%)
	Rural	40(63.49%)	34(53.97%)
	Total	63(100%)	63(100%)

Table 4: Comparison of duration of Motor blockages between Ropivacaine and Bupivacaine groups

Groups	Duration of Motor Blockages		Independent t-test P-Value
	N	Mean±SD	
Bupivacaine	63	189.33±11.947	0.0001
Ropivacaine	63	120.89±12.122	

Table 5: Comparison of duration of Sensory blockages between Ropivacaine and Bupivacaine groups

Groups	Duration of Sensory Blockages		Independent t-test P-Value
	N	Mean±SD	
Bupivacaine	63	190.2±8.39	0.0001
Ropivacaine	63	153.8±9.3	

Table 6: Stratification of duration of Motor blockages between between Ropivacaine and Bupivacaine groups with regards to age 18-45 and 46-60 years.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
18-45	Bupivacaine	35/63	193.33±18.947	0.0001
	Ropivacaine	40/63	126.09±10.12	
46-60	Bupivacaine	28/63	199.65±20.47	0.0001
	Ropivacaine	23/63	109.89±25.122	

Table 7: Stratification of duration of Sensory blockages between between Ropivacaine and Bupivacaine groups with regards to age 18-45 and 46-60 years.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
18-45	Bupivacaine	35/63	205.75±21.09	0.0001
	Ropivacaine	40/63	163.91±19.312	
46-60	Bupivacaine	28/63	197.25±15.39	0.0001
	Ropivacaine	23/63	160.21±11.82	

Table 8: Stratification of duration of Motor blockages between between Ropivacaine and Bupivacaine groups with regards to female and male.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
Female	Bupivacaine	25/63	196.04±17.47	0.0001
	Ropivacaine	31/63	134.89±12.26	
Male	Bupivacaine	38/63	189.33±11.947	0.0001
	Ropivacaine	32/63	120.89±12.122	

Table 9: Stratification of duration of Sensory blockages between between Ropivacaine and Bupivacaine groups with regards to female and male.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
Female	Bupivacaine	25/63	211.2±28.3	0.0001
	Ropivacaine	31/63	167.8±14.3	
Male	Bupivacaine	38/63	193.2±18.8	0.0001
	Ropivacaine	32/63	158.8±9.3	

Table 10: Stratification of duration of Motor blockages between between Ropivacaine and Bupivacaine groups with regards to Urban and Rural regions.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
Urban	Bupivacaine	29/63	198.3±13.5	0.0001
	Ropivacaine	23/63	126.9±12.5	
Rural	Bupivacaine	34/63	199.9±19.0	0.0001
	Ropivacaine	40/63	130.9±12.7	

Table 11: Stratification of duration of Sensory blockages between between Ropivacaine and Bupivacaine groups with regards to Urban and Rural regions.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
Female	Bupivacaine	29/63	194.2±18.4	0.0001
	Ropivacaine	23/63	159.8±9.3	
Male	Bupivacaine	34/63	201.2±18.3	0.0001
	Ropivacaine	40/63	173.8±19.1	

Table 12: Stratification of duration of Motor blockages between between Ropivacaine and Bupivacaine groups with regards to BMI.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
BMI(<24kg/m2)	Bupivacaine	30/63	196.53±16.947	0.0001
	Ropivacaine	35/63	130.89±17.122	
BMI(>24kg/m2)	Bupivacaine	33/63	199.33±11.947	0.0001
	Ropivacaine	28/63	126.019±13.22	

Table 13: Stratification of duration of Sensory blockages between between Ropivacaine and Bupivacaine groups with regards to BMI.

Age	Groups	Duration of Motor Blockages		Independent t-test P-value
		N	Mean±Sd	
BMI(<24kg/m2)	Bupivacaine	30/63	196.25±19.279	0.0001
	Ropivacaine	35/63	163.81±11.312	
BMI(>24kg/m2)	Bupivacaine	33/63	180.25±28.34	0.0001
	Ropivacaine	28/63	159.54±19.02	

DISCUSSION

The findings of the previous research^{8,9} showing ropivacaine may generate predictable and dependable spinal anaesthesia for a variety of surgical procedures have been verified by the current investigation⁷. The results of the current study differ from those of the two previous clinical investigations, which reported blockades with ropivacaine that are inappropriate for surgery^{2, 9}. The difference might be caused by the fact that these writers employed ropivacaine glucose-free solutions¹⁰. The difference demonstrates that ropivacaine solution with glucose added has the same effects as other medications¹,

¹¹. In the current investigation, the ropivacaine group had a delayed start of sensory and motor blockage compared to the bupivacaine group. Moreover, the ropivacaine group's total period of sensory and motor blockage was shorter than the bupivacaine group's. This result is consistent with those of Erturk et al.¹² and Bigat et al.¹³. This could be as a result of bupivacaine's somewhat stronger protein binding and higher lipid solubility when compared to ropivacaine. An significant factor in local anaesthetic action is lipid solubility^{8, 14}. The local anesthetic's lipid solubility has a direct correlation with the conduction block's onset time. The

sequestration of the local anaesthetic in myelin and other nearby neuronal compartments is increased by increased lipid solubility¹⁵. As a result, the impact is increased since the gradual release of the local anaesthetic is made possible by the depot that is created when the local anaesthetic molecule is absorbed into the myelin and adjacent neuronal compartments^{16,17}. In general, the longer-acting and more lipid-soluble substances have higher protein binding. Compared to the more lipid-soluble bupivacaine, ropivacaine may penetrate the big myelinated A fibres more slowly because of its reduced lipid solubility¹⁷. Moreover, it is hypothesised that ropivacaine affects unmyelinated pain fibres more strongly than myelinated motor fibres because it is less lipophilic¹⁸. No late effects, such as back discomfort or other temporary symptoms, were seen, which is consistent with other research on the use of ropivacaine spinal bupivacaine in spinal anaesthesia^{11,19}. Both groups experienced comparable intraoperative and postoperative side symptoms (bradycardia, nausea, cold, and vomiting)²⁰. Our research did have certain limitations, though. One of the drawbacks was that blinding, which would have produced some bias, wasn't done. Moreover, we did not standardise the dosage according to the patient's age, height, or weight. Hyperbaric blood pressure has historically been the preferred medication for spinal anaesthesia, a conventional method frequently utilised for numerous lower extremities procedures²¹. Yet, as shown by a number of studies, RP has emerged as a suitable substitute due to its reduced cardio- and neurotoxic profile²². It has been demonstrated that intrathecal RP causes more efficient local anaesthesia in dogs than intrathecal BP²³. Hence, different studies have shown that intrathecal RP is successful in a variety of surgical procedures, including total hip arthroplasty, transurethral prostate

excision, pelvic and limb operations²⁴. Both groups showed variance in the distribution of the sensory block, which they hypothesised may be caused by the adoption of a straightforward fix²⁵. This study was conducted to evaluate the efficacy of intrathecal administration of hyperbaric RP and hyperbaric BP in terms of the onset and duration of effective anaesthesia and analgesia. This supports the findings of Chung et al., who discovered that the RP group required more time than the BP group to attain T10, the highest level of sensory blockage ($p < 0.05$)²⁶. The study's patient placement and anaesthetic dosages were intended to primarily accomplish sensory block and prevent lower extremity motor block. Several publications claim that smaller dosages of hypobaric bupivacaine or lidocaine were utilised for ventral pressure ulcers with good sensory block and minimal motor block. Motor block was absent in 135 (90%) of the patients²⁷. None of the individuals in the current research needed a urinary catheter. 6 mg of hypobaric 0.15% bupivacaine takes 105 minutes to recover from. The recovery time was decreased to 99 minutes by changing the hypobaric dosage from 0.15% bupivacaine to 4.5 mg²⁸. The recovery time for 40 mg of lidocaine in the 1% solution is 142 minutes. The recovery period for the same dosage of 0.5% hypobaric lidocaine was 151 minutes. Similar to the current investigation, recovery following 18 mg of hypobaric 0.6% lidocaine took 63 minutes (64 minutes). Comparing lidocaine to bupivacaine in this study, a shorter recovery time was statistically significant²⁹. When the conventional spinal block was compared to the asymmetric spinal block, it was found that one of the purposes of the posterior spinal block was to decrease the incidence of hypotension that can happen with this procedure. Due to the jack-knife posture and little sympathetic blocking, the hypobaric

solution stayed isolated at the injection site, which is likely what caused the hemodynamic stability³⁰. With all anaesthetics, spinal blocks have been associated with transient neurological effects. No patients in the current research experienced temporary neurological symptoms that differed from those seen with greater dosages, supporting the significance of low doses in this investigation.

CONCLUSION

The results of this study show that, in comparison to ropivacaine, intrathecally administered bupivacaine causes sensory block to occur more quickly and last longer. This finding has important implications for clinical practice, particularly in the context of regional anaesthesia for surgical and postoperative pain management. Despite the fact that both medications are often used for intrathecal anaesthesia, the findings of this study indicate that bupivacaine could offer better pain alleviation and a quicker beginning of effect. However, more investigation is required to thoroughly assess the relative efficacy and safety of these two medications, particularly in light of long-term effects and negative side effects. Overall, the results of this study suggest that bupivacaine may represent a promising option for intrathecal anaesthesia and warrant further investigation in future clinical trials.

Ethics Approval: The ERC gave ethical review approval

Consent To Participate: written and verbal consent was taken from subjects and next of kin

Funding: The work was not financially supported by any organization. The entire expense was taken by the authors

Acknowledgements: We are thankful to all who were involved in our study.

Authors' Contributions: All persons who meet authorship criteria are listed as authors, and all authors certify that they have

participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

Conflict Of Interest: No competing interest declared.

REFERENCES

1. Lee J-K, Park JH, Hyun S-J, Hodel D, Hausmann ON. Regional anesthesia for lumbar spine surgery: can it be a standard in the future? *Neurospine*. 2021;18(4):733.
2. Folino TB, Mahboobi SK. *Regional Anesthetic Blocks*. 2020.
3. Mancel L, Van Loon K, Lopez AM. Role of regional anesthesia in Enhanced Recovery After Surgery (ERAS) protocols. *Current Opinion in Anesthesiology*. 2021;34(5):616-25.
4. Imbelloni L, Gouveia M, Ghorayeb N, Neto S. Spinal anesthesia: much more than single shot of hyperbaric bupivacaine. *Int J Anesthesiol*. 2021;8(1):122.
5. Shamkumar S. A randomised controlled study comparing intrathecal hyperbaric bupivacaine-fentanyl mixture and isobaric bupivacaine-fentanyl mixture in common urological procedures: Thanjavur Medical College, Thanjavur; 2018.
6. Rattenberry W, Hertling A, Erskine R. Spinal anaesthesia for ambulatory surgery. *BJA education*. 2019;19(10):321.
7. Hungund S, Hirolli DA, Bhosale R, Thilakchand K. Comparison Of Epidural-Fentanyl And Levobupivacaine With Fentanyl And Bupivacaine For Lower Abdominal And Lower Limb Surgeries--A Prospective Study. *Journal of Evolution of Medical and Dental Sciences*. 2018;7(11):1380-5.

8. Olawin AM, Das JM. Spinal anesthesia. StatPearls [Internet]: StatPearls Publishing; 2021.
9. Marhofer P, Columb M, Hopkins PM, Greher M, Marhofer D, Bienzle M, et al. Dexamethasone as an adjuvant for peripheral nerve blockade: a randomised, triple-blinded crossover study in volunteers. *British journal of anaesthesia*. 2019;122(4):525-31.
10. Chen N, Qiao Q, Chen R, Xu Q, Zhang Y, Tian Y. The effect of ultrasound-guided intercostal nerve block, single-injection erector spinae plane block and multiple-injection paravertebral block on postoperative analgesia in thoracoscopic surgery: A randomized, double-blinded, clinical trial. *Journal of clinical anaesthesia*. 2020;59:106-11.
11. Tarkase A. Spinal Anaesthesia With 0.5% Hyperbaric Ropivacaine and 0.5% Hyperbaric Bupivacaine: A Comparative Study. 2020.
12. Sethi D. Randomised control trial comparing plain levobupivacaine and ropivacaine with hyperbaric bupivacaine in caesarean deliveries. *Turkish Journal of Anaesthesiology and Reanimation*. 2019;47(6):471.
13. Badenes R, Nato CG, Peña JD, Bilotta F. Inhaled anesthesia in neurosurgery: Still a role? *Best Practice & Research Clinical Anaesthesiology*. 2021;35(2):231-40.
14. Barletta M, Reed R. Local anesthetics: pharmacology and special preparations. *Veterinary Clinics: Small Animal Practice*. 2019;49(6):1109-25.
15. Elsharkawy H, Kolli S. Pharmacology of Local and Neuraxial Anesthetics. *Basic Sciences in Anesthesia*. 2018:161-76.
16. Taylor A, McLeod G. Basic pharmacology of local anaesthetics. *BJA education*. 2020;20(2):34.
17. Grage SL, Culetto A, Ulrich AS, Weinschenk S. Membrane-mediated activity of local anesthetics. *Molecular Pharmacology*. 2021;100(5):502-12.
18. Srinivasan E. Comparison of Levobupivacaine and Levobupivacaine with Fentanyl in Infraumbilical Surgeries under Spinal Anaesthesia: Madras Medical College, Chennai; 2020.
19. Singh P, Kapur A, Gupta SK. Comparative evaluation of low-dose levobupivacaine and ropivacaine in patients undergoing inguinal herniorrhaphy under walking spinal anaesthesia as daycare surgery. *Bali Journal of Anesth*. 2019;3:111-7.
20. Imbelloni LE, Braga RL, de Morais Filho GB, Da Silva A. Low dose of isobaric bupivacaine provides lower incidence of spinal hypotension for hip surgery in elderly patients. *Anaesthesia, Pain & Intensive Care*. 2019:17-20.
21. Shah N, Kumari A, Behl A, Desai J, Shah A, Chauhan D. A study to compare the effect of nalbuphine and butorphanol as an adjuvant to intrathecal 0.5% hyperbaric bupivacaine for lower limb surgery. *International Journal of Health Sciences*. (I):3887-96.
22. Prajapati H, Pander K, Chavda A, Upadhya M. Effectiveness Of 2% Isobaric In Producing Spinal Anaesthesia In Comparison to 5% Heavy Xylocaine. *National Journal of Integrated Research in Medicine*. 2019;10(6).
23. Saiyad JH, Patel SK, Patel US. A Comparison of Dexmedetomidine and Fentanyl as an Adjuvant to Intrathecal Hyperbaric Bupivacaine in Elective Lower Limb Surgeries. *National Journal of Medical Research*. 2021;11(04):125-30.
24. Ponde V. Recent trends in paediatric regional anaesthesia. *Indian journal of anaesthesia*. 2019;63(9):746.

25. Hu J. Angulins and the Tricellular Tight Junction: Role in Inflammatory Bowel Diseases 2021.
26. Shreyas S, Totawar S, Malshetwar K. Effects of Intrathecal Isobaric Ropivacaine with Fentanyl Versus, Hyperbaric Bupivacaine with Fentanyl in Elective Inguinal Hernia Surgeries. *European Journal of Molecular & Clinical Medicine (EJMCM)*.10(01):2023.
27. Chapron K, Sleth JC, Capdevila X, Bringuier S, Dadure C. Hyperbaric prilocaine vs. hyperbaric bupivacaine for spinal anaesthesia in women undergoing elective caesarean section: a comparative randomised double-blind study. *Anaesthesia*. 2021;76(6):777-84.
28. Almeida CR, Cunha P, Vieira L, Gomes A. Low-dose spinal block for hip surgery: A systematic review. *Trends in Anaesthesia and Critical Care*. 2022.
29. Vinoth E. A Prospective Randomized Controlled study Comparing Intrathecal Midazolam Versus Fentanyl Citrate as an Adjuvant to 0.5% Bupivacaine Heavy in Spinal Anaesthesia for Infraumbilical Surgeries: ESIC Medical College & PGIMS & R, Chennai; 2020.
30. Ashwini B. A Comparison of Bupivacaine with Buprenorphine Versus Bupivacaine with Fentanyl in Spinal Anaesthesia at a Tertiary Care Hospital: A Cross Sectional study: Sree Mookambika Institute of Medical Sciences, Kulasekharam; 2020.