

Clinical Evaluation of Levobupivacaine in Subarachnoid Block - A Randomized, Double Blind, Controlled Study with Bupivacaine

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Abstract: ***Aim:** To evaluate the characteristics of subarachnoid block with levobupivacaine and bupivacaine. **Materials and Methods:** 100 adult patients scheduled for lower limb orthopaedic surgery were allocated in two groups of 50 each. Group- A received 0.5% isobaric Bupivacaine 3.0 ml, Group-B 0.5% isobaric Levobupivacaine 3.0ml. **Results:** Mean time to onset and peak of sensory blockade for highest sensory level was and 11.61 ± 03.44 min and 12.75 ± 03.56 min respectively in group A and 12.00 ± 02.64 min and 13.08 ± 02.67 min respectively in group B. Mean time to achieve motor blockade modified Bromage scale III was 10.13 ± 02.86 min in group A and 10.64 ± 02.76 min resp. in group B. The mean duration of sensory and motor blockade was 378.08 ± 50.63 min and 271.19 ± 17.09 min in group A and 381.6 ± 42.87 min and 272.96 ± 25.21 min in group B. The mean duration of postoperative analgesia in group A and group B was 378.08 ± 50.63 min and 381.6 ± 42.87 min resp. The duration of sensory blockade was prolonged in group B compare to group A but it was not statistically significant. Hemodynamic variables and SpO₂ remained within normal limit and were comparable in both groups. **Conclusion:** Bupivacaine and levobupivacaine in subarachnoid blockade are equally effective and safe with comparable onset, peak, and duration of sensory and motor blockade and post operative analgesia. It can be concluded that levobupivacaine seems to be an interesting alternative to bupivacaine for spinal anaesthesia.*

Keywords: Levobupivacaine, Bupivacaine, Subarachnoid Blockade, isobaric, orthopaedic surgery

1. Introduction

Subarachnoid block is a type of regional anaesthesia in which there is reversible interruption of nerve transmission following injection of local anaesthetic solution into subarachnoid space. It has the advantage of simplicity of technique, rapid onset of action, reliability in producing uniform sensory and motor blockade, reducing stress response of surgery and incidence of deep vein thrombosis, minimising blood loss and is cheaper as compared to general anaesthesia for lower abdomen and lower limb surgeries.

Severe central nervous system (CNS) and cardiovascular adverse reaction reported in the literature after inadvertent intravascular injection or intravenous regional anaesthesia has been linked to the R (+) isomer of bupivacaine.^[1] (S-) bupivacaine has been recognised as a lesser toxic of this compound's two enantiomers.^[2,3] Its less cardiovascular and central nervous system toxicity, makes levobupivacaine a less toxic substitute for bupivacaine.^[4-9]

Levobupivacaine (S-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride), the pure S (-) enantiomer of racemic bupivacaine, is a new long -acting local anaesthetic that has recently been introduced in the clinical routine.^[10-13] The levorotatory isomers were shown to have a safer pharmacological profile^[11,14] with less cardiac^[4-8] and neurotoxic^[6,8] adverse effect. The decreased toxicity of levobupivacaine is attributed to its faster protein binding rate.¹⁵

Because of their close chemical relationship, levobupivacaine and racemic bupivacaine share many pharmacokinetic properties; therefore, it is not surprising

that the preliminary clinical experiences show that both local anaesthetics are largely equally effective.

2. Review of Literature

The techniques of neuroaxial anaesthesia in men are less than 100 years old and have been taught widely only since 1950. The important advances in the development of neuraxial anaesthesia are summarized as follows:

- 1) 1764 Domenico Cotugno^[16] discovered cerebrospinal fluid
- 2) 1825 Magendie^[17] described circulation of cerebrospinal fluid
- 3) 1853 Alexander Wood^[18] developed hypodermic syringe and needle
- 4) 884 Cocaine used for topical anaesthesia for eye by Koller^[19]
- 5) 1885 J. Leonard Corning,^[20] a neurologist, inadvertently administered first spinal anaesthesia. He appears to have regarded the intentional Intrathecal injection only as a means of alleviating existing pain. He overlooked its possibilities in surgery.
- 6) 1891 Quincke^[21] described the technique of lumbar puncture as a simple clinical procedure.
- 7) 1898 August Bier^[22] gave first planned spinal anaesthesia for surgery in man on 16 August 1898 by injecting 3ml of 0.5% cocaine. He described 6 cases conducted with spinal analgesia for lower limb surgery. He was later named as father of spinal anaesthesia.
- 8) 1904 Bain Bridge^[23] was the first who advocate spinal analgesia in paediatric surgery. The youngest patient was 3 months old child with bilateral inguinal hernia.

- 9) Alley et al ^[24] in 2002 conducted a double-blinded, randomized, cross-over study to compare the clinical efficacy of hyperbaric levobupivacaine and bupivacaine for spinal anaesthesia. Eighteen healthy volunteers were randomized into three equal groups to receive two spinal anaesthetics, one with bupivacaine and the other with levobupivacaine, of equal-milligram doses (4, 8, or 12 mg). They concluded that hyperbaric spinal levobupivacaine has equivalent clinical efficacy to racemic bupivacaine for spinal anaesthesia in doses from 4 to 12 mg.
- 10) In 2002, Christian Glaser, et al^[25] carried out a prospective randomized double-blinded study to evaluate the anaesthetic potencies and hemodynamic of Intrathecal levobupivacaine compared with racemic bupivacaine. Eighty patients undergoing elective hip replacement received either 3.5mL levobupivacaine 0.5% isobaric or 3.5mL bupivacaine 0.5% isobaric. We conclude that intrathecal levobupivacaine is equal in efficacy to, but less toxic than, racemic bupivacaine.
- 11) In 2003, Lee YY, Muchhal K, Chan CK et al ^[26] carried out this prospective, randomized, double-blind study compared the clinical efficacy and motor block of 0.5% levobupivacaine with 0.5% racemic bupivacaine in spinal anaesthesia for urological surgery. Fifty patients were recruited (levobupivacaine group n =24; bupivacaine group n = 26). Spinal anaesthesia was achieved with 2.6 ml of study solution injected in the subarachnoid space. There were no significant differences between the two groups in the quality of sensory and motor block or in hemodynamic change. They concluded that 0.5% levobupivacaine can be used as an alternative to 0.5% racemic bupivacaine in spinal anaesthesia for surgery when a sensory block to at least T10 is required.
- 12) Opas Vanna et al ^[27] in 2006 had carried out study to investigate the clinical efficacy and safety of isobaric solution of levobupivacaine compared with hyperbaric solution of racemic bupivacaine in spinal anaesthesia. The authors studied 70 patients undergoing elective transurethral endoscopic surgery. The present study indicated that 2.5 ml of 0.5% isobaric levobupivacaine and 0.5% hyperbaric of racemic bupivacaine show equally effective potencies for spinal anaesthesia, regard to both the onset time and duration of sensory blockade.
- 13) [13] In 2009, H. Sen. ^[29] carried out a study to compare the efficacy of hyperbaric and isobaric solution of Intrathecal levobupivacaine for transurethral endoscopic surgery. The heavy group received 13.5mg of hyperbaric Levobupivacaine while the plain group received 13.5mg isobaric levobupivacaine both intrathecally in a 3ml total volume. They concluded that the clinical efficacy of hyperbaric levobup vacaine was superior to isobaric form in spinal anaesthesia for transurethral resection.
- 14) [14] In 2011 Sathitkarnmanee T et al ^[32] comparison of spinal isobaric levobupivacaine and racemic bupivacaine for lower abdominal and lower abdominal and lower extremity surgery. They received either 0.5% isobaric racemic bupivacaine 3ml or 0.5% isobaric levobupivacaine 3ml for spinal anaesthesia. Study indicated that 15 mg of isobaric racemic bupivacaine and levobupivacaine for spinal anaesthesia had equivalent peak block height and showed equally effective efficacy

regarding to both the onset time and duration of motor and sensory blockade.

- 15) Gulen Guler et al ^[33] in 2012 had carried out study to investigate the clinical efficacy of levobupivacaine compared with hyperbaric bupivacaine for spinal anaesthesia for caesarean section. 60 Pregnant women in ASA I - II group scheduled to have elective caesarean operation were allocated into the study. The combinations 10 mg levobupivacaine (0.5%) + fentanyl (15 µg) for Group LF (n = 30) patients, 10 mg hyperbaric bupivacaine (0.5%) + fentanyl (15 µg) for BF (n = 30) patients were intrathecally administered a total of 2.3 cc.. It was observed that in Group BF, the evolution of the motor block was faster and lasted longer. Whereas hypotension, bradycardia and nausea were less in Group LF, the need for ephedrine was higher in Group BF (p < 0.05). Since motor block time is shorter, and side effects like hypotension, bradycardia and nausea are less, the combination of levobupivacaine + fentanyl can be a good alternative in caesarean sections.

3. Material and Methods

After Institutional Review Board approval and informed written consent, this prospective randomized double blind controlled clinical study was carried out in 100 patients, aged 20 to 60 years belonging to ASA physical status I and II, undergoing elective lower limb surgery under subarachnoid blockade.

<i>Inclusion Criteria:</i>	<i>Exclusion Criteria:</i>
[1] Informed written consent for participation in study.	[1] Contraindication to spinal anaesthesia (refusal of patient, local site infection, coagulation disorders, spine deformity).
[2] Aged 30 to 60 years of either sex.	[2] Allergy to local anaesthetic or study drug.
[3] ASA physical status I and II.	[3] Patients taking any analgesics, anticoagulants.
[4] Patients posted for lower limb surgery.	[4] Patients with arrhythmias.
[5] BMI ≤ 30kg/m ² .	[5] Patients with psychiatric /neurological disorders. Antenatal female.

All the patients were subjected to detailed pre-anaesthetic evaluation with clinical history and systemic examination. Routine investigations like Haemogram, Random Blood Sugar, Renal Profile, and ECG for patients above 40 years of age were done.

To get desired sample size by conducive sampling method, 100 patients were taken to assess my hypothesis. Randomization was done by using computer generated randomization software. According to that patients were allotted in groups. . One member of the team filled up the drug as per the group assigned. Principle investigator performed subarachnoid block and responsible for monitoring of patient.

- Group A: (n=50) Patients received 3.0 ml of 0.5 % isobaric levobupivacaine**
- Group B: (n=50) Patients received 3.0 ml of 0.5 % isobaric bupivacaine**

Preoperatively, adequate fasting hours (6-8 hours) ensured. Each patients were informed in detail regarding the nature, purpose of the study and explained 0-10 point visual analogue scale (VAS) on paper sheet where (0) labelled as (no pain) and (10) as (excruciating pain). Written informed consent was obtained after explaining the procedure to the patient. Patients who with inadequate sensory and motor blockade required supplementation were excluded from the study. In pre anesthesia preparation room, Baseline vital parameters (Heart rate, blood pressure, respiratory rate, SpO₂) were recorded. Intravenous line was secure on contra lateral arm with 18G cannula and the patient was premeditated with midazolam 0.015mg/kg intravenously 15min prior to procedure. Then patient was shifted to Operation Theater. In the operation theater, Preloading was done with inj. Ringer lactate 15ml/kg. Subarachnoid block was performed in the left lateral position with 25 gauge spinal needle in L3-L4 inter space with full aseptic and antiseptic precautions and the drug was injected as per the group assigned. Doctor who was performing the block remained blinded to the content of the solution. Immediately after the block, patient was turned supine and assessed for sensory and motor characteristics of block as per the grading shown in the tables (Table no. 2) at every 30 seconds interval till peak effect is achieved. The sensory block was assessed by skin sensation to pin prick (23 G hypodermic needle). The motor block was assessed according to the Modified Bromage Scale (Table no.3). Time to onset of sensory block at L1, T10, and maximum level attained were noted.

Table 1: Sensory and Motor Characteristics of Subarachnoid Block

	Onset	Peak	Duration
sensory block	dull response to pin prick.	no response to pin prick.	onset of block to VAS ≥ 5
motor block	Bromage scale grade I of motor block.	Bromage scale grade III motor block.	regression of motor block to previous level

Table 2: Modified Bromage Scale for Motor Block

Grade 0	The patient is able to move the hip, knee and ankle.
Grade I	The patient is unable to move the hip but is able to move the knee and ankle.
Grade II	The patient is unable to move the hip and knee but able to move the ankle.
Grade III	The patient is unable to move the hip, knee and ankle.

Hemodynamic variables were recorded at 1, 3, 5, 10, 15, 20, 30 minutes and then at 15 minutes interval throughout the surgical period. Hypotension was defined as a decrease in systolic blood pressure > 30% of the baseline value, and treated with crystalloid fluid and intravenous Inj. Mephentermine 5mg if required. Bradycardia was defined as a pulse rate of < 60 beat/ min and treated with 0.3-0.5 mg atropine. Intra operatively sedation score was assessed at every 15 minutes interval. Any supplementation required and other complications like nausea, vomiting, pruritus were recorded. After the completion of surgery, patient was shifted to Post Anaesthesia Care Unit (PACU), and sensory and motor block were be assessed 30 minutes interval till regression of sensory and motor blockade. Thereafter patient was monitored at 4 hourly interval for next 24 hours for

complications. Supplemental analgesic (inj. diclofenac sodium 75mg intravenously) was given at VAS ≥ 5.

Outcome Measures

Sensory and motor blockade characteristics in the form of onset, peak, regression of sensory and motor block. Supplemental analgesia required postoperatively (Inj. diclofenac 75 mg IV at VAS ≥ 5). Hemodynamic parameters were assessed and monitored up to 24 hour. Postoperative complications like nausea, vomiting, hypotension, bradycardia, respiratory depression and neurological complications were observed.

Statistical Methods

Data was expressed as mean and standard deviation or numbers and percentages as applicable. Comparison between two groups were done using mann whitney test for quantitative data and chi square test for Qualitative data. P value < 0.05 was considered significant.

4. Observation and Results

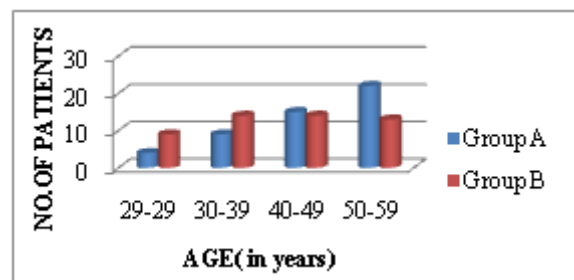
Findings of this study are as under:

Table 1: Patients Characteristics in two Groups

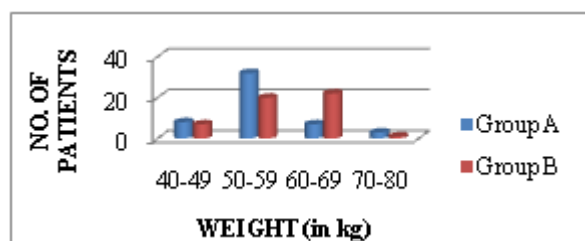
Demographic Variables	Group A Mean ± SD	Group B Mean ± SD	P value
Age(years)	44.10 ± 09.04	41.20 ± 08.69	> 0.05
Weight(kg)	56.20 ± 06.47	57.46 ± 06.54	> 0.05
Height(m)	158.20 ± 05.23	157.00 ± 05.37	> 0.05
ASA Physical Status I/II	22 / 28	32 / 18	> 0.05

Inference: Patients characteristics in terms of age, weight, and height and ASA physical status were comparable among the two groups of patients. (P > 0.05)

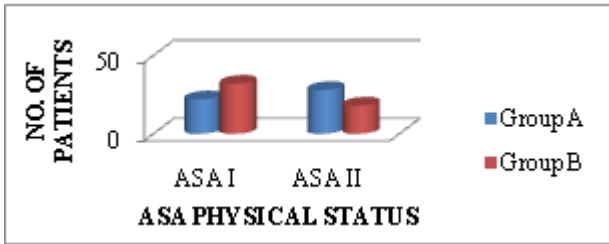
Demographic Profile of Patients in Three Groups



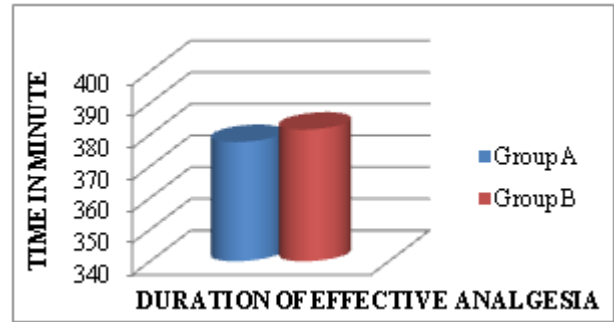
Bar diagram 1A: Distribution of patients in respect to age



Bar diagram 1B: Distribution of patients in respect to weight

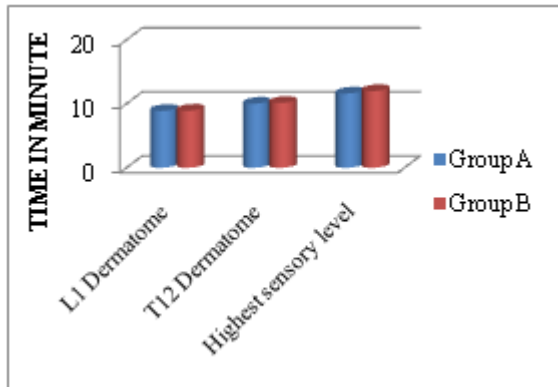


Bar diagram 1C: Distribution of patients in respect to ASA Physical status

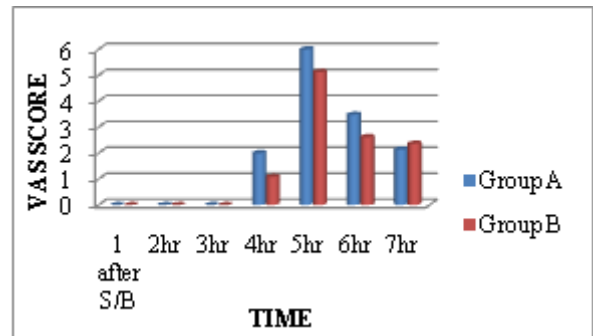


Bar diagram 3: Duration of effective analgesia
Inference: On comparison of group A with group B there was no significant difference in regard to duration of effective analgesia.

Sensory Characteristics of Subarachnoid Block

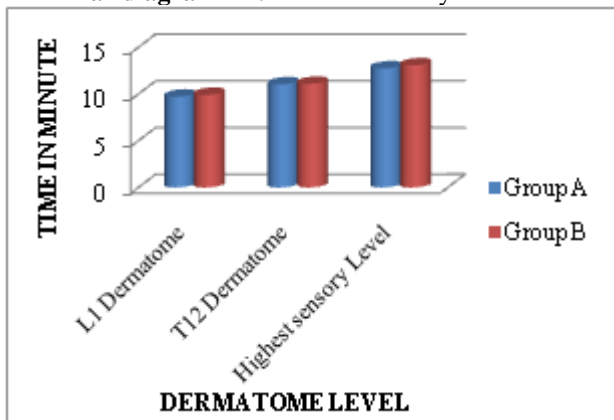


Bar diagram 2A: Onset of sensory blockade

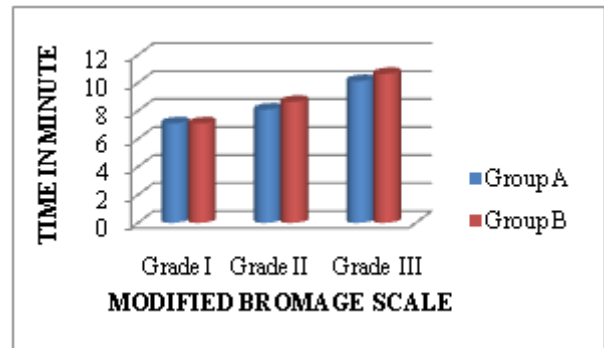


Bar diagram 4: Visual Analogue Scale and time of first rescue analgesic required

Inference: The first rescue analgesic was required within 5 hrs in group A and group B. There was no significant difference between both groups.

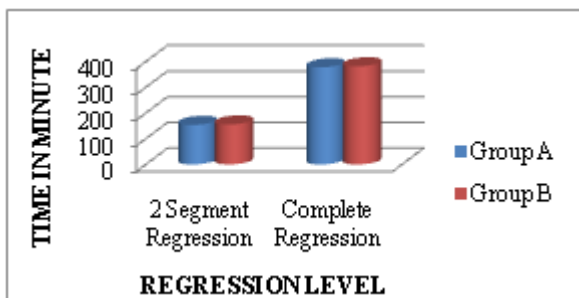


Bar diagram 2 B: Time to reach peak of sensory blockade



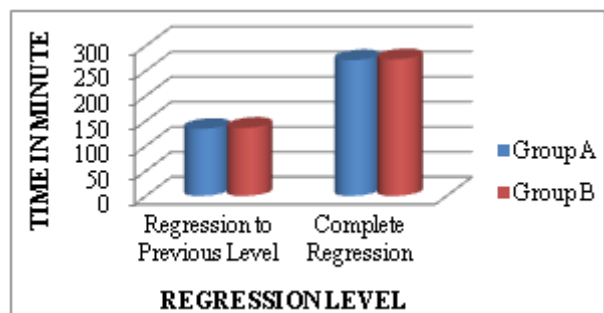
Bar diagram 5A: Onset of motor blockade

Inference: The difference in mean time for onset and duration of motor blockade was not significant in group A and group B.

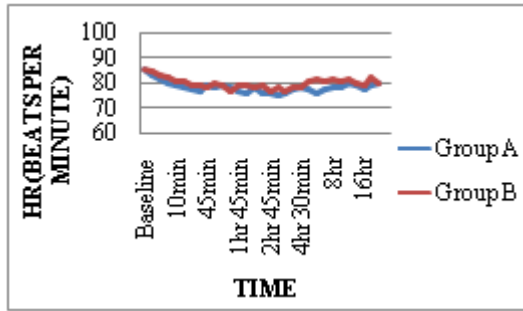


Bar diagram 2C: Time for regression of sensory blockade

Inference: The difference in mean time for onset, peak and duration of sensory blockade in these two groups was not significant. ($P > 0.05$)

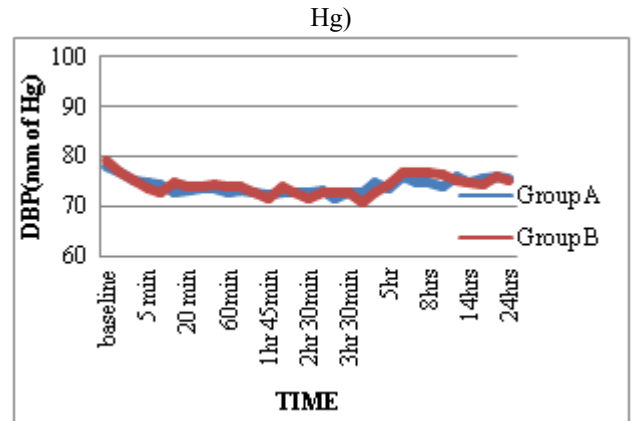


Bar diagram 5 B: Regression of motor blockade

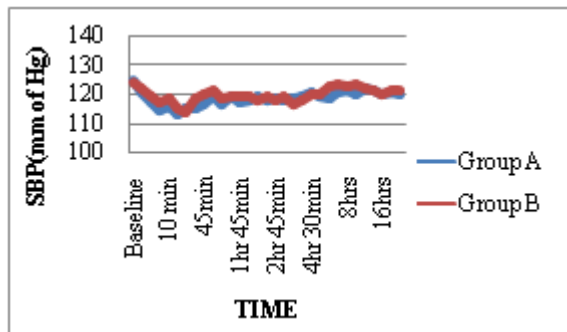


Line diagram 1: Changes in heart rate

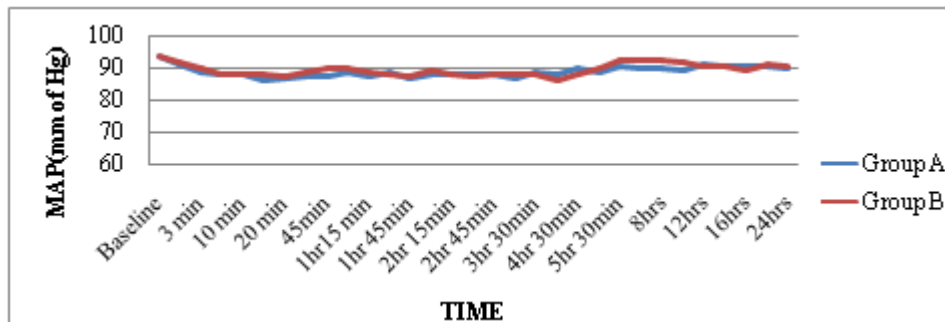
Inference: The changes observed in heart rate were comparable between two groups throughout the study period.



Line diagram 2B: Changes in Diastolic blood Pressure (mm Hg)



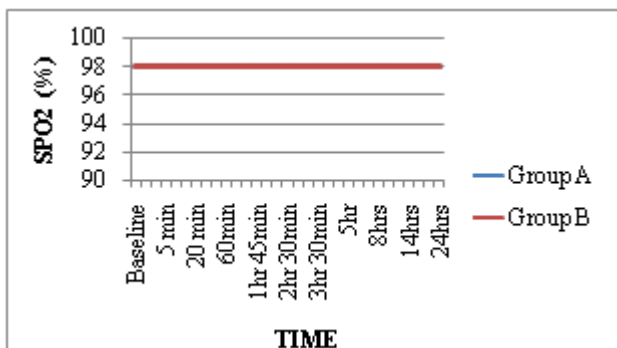
Line diagram 2A: Changes in Systolic blood Pressure (mm Hg)



Line diagram 2C: Changes in mean arterial blood Pressure (mm Hg)

Inference: There was significant decrease in SBP, DBP, and MAP from base line

Line diagram 3 : Changes in SpO₂



Inference: The changes observed in heart rate were comparable between two groups throughout the study period.

Table 10: Complications

Complications	Group A		Group B	
	No. of pts	%	No. of pts	%
Nausea/Vomiting	00	00	00	00
Hypotension	00	00	00	00
Bradycardia	00	00	00	00
Respiratory depression	00	00	00	00
Neurological complications	00	00	00	00

Inference: None of the patient in either group developed any complication, through the study period.

5. Discussion

Subarachnoid block is a popular mode of anaesthesia for lower abdominal and lower limb surgery. It has several advantages like easy to perform and reliable, provide excellent operating conditions for the surgeon, less costly, maintains a patent airway, decreases pulmonary complications, decreases incidences of deep vein thrombosis

and pulmonary emboli compared to general anaesthesia and returns faster gastro intestinal function as compared to general anaesthesia. There is also decreases intensity of stress response to anaesthesia and surgery and decreased blood loss during surgery.

There are various local anaesthetic agents available in the market and currently Bupivacaine is the most commonly used local anaesthetic worldwide due to its longer duration of action.

Levobupivacaine is S (-) enantiomer of racemic bupivacaine. The affinity of the S(-) isomer to the cardiac sodium channel in the inactive state is lower than that of R(-) isomer. Its pharmacokinetics properties are similar to those of racemic bupivacaine. Because of the lower degree of toxicity when compared, in particular to racemic bupivacaine, its introduction into clinical practice as a new local anaesthetic levobupivacaine has been pointed out. In the past, several authors had already investigated such advantageous characteristics, either in the animal or humans, emphasizing the association of levobupivacaine to a higher convulsive threshold and to a lower influence on cardiac or stroke indexes and ejection fraction.^{4,6,8} Several studies indicate that its faster protein binding rate suggest a lower degree of toxicity.⁹ Levobupivacaine is considered as a good alternative to bupivacaine because of its lower side effects on cardiovascular and central nervous system.

The majority of the clinical studies that have compared levobupivacaine and bupivacaine have discovered few differences between them and report that both anaesthetics perform similarly. If levobupivacaine has been already investigated when used for epidural and loco-regional procedures, more has to be known as regard its clinical features in subarachnoid block. To this purpose Glaser et al²⁶ in their randomized, double-blind prospective study, compared isobaric solutions (3.5ml of 0.5% levobupivacaine; 3.5ml of 0.5% bupivacaine) in 80 patients undergoing elective hip replacements under subarachnoid block. These authors found no clinical differences and concluded that both drugs were equipotent and offered similar durations, onset times, and degrees of motor and sensory blockades.

After comparing 3 ml of 0.5% spinal bupivacaine and levobupivacaine for hip surgery, Fattorini et al³³ found that there were no significant differences in subarachnoid blockade characteristics. Sathitkarnmanee et al³⁷ conducted a study with 70 patients to compare 0.5% isobaric levobupivacaine (3ml) versus 0.5% isobaric bupivacaine (3ml) for elective lower limb and lower abdominal surgery with subarachnoid blockade. These authors showed no significant differences in the quality of motor and sensory blockades between both groups.

Lee et al¹²⁶ undertook a study which included 50 patients awaiting urological surgery under subarachnoid blockade. These authors employed 2.6ml of 0.5% isobaric solution of levobupivacaine and bupivacaine and reported no significant differences. Vanna et al³⁰ compared 0.5% hyperbaric bupivacaine and 0.5% isobaric levobupivacaine, 2.5ml for both, for elective transurethral endoscopic surgery. They

showed equally effective potencies for subarachnoid blockade in both sensory blockade onset time and duration terms.

Cuvas et al¹⁴⁶ and Alley et al¹²⁴ studied isobaric levobupivacaine and hyperbaric bupivacaine of same concentration but in different doses. They showed equal potencies for subarachnoid blockade as far as sensory blockade duration and onset times are concerned. Similar to our study but with lower dose, Monica Del-Rio-vellosillo¹³⁵ compared isobaric bupivacaine and levobupivacaine in subarachnoid blockade. They concluded that Isobaric bupivacaine and levobupivacaine are analogous and well-tolerated anaesthetics for knee arthroscopy. However, for bupivacaine, sensory and motor blockade onset was faster, and greater sensory blockade with a longer postoperative painless period was achieved.

Many other studies have performed the comparison between these two drugs either isobaric form or hyperbaric form, found no significant difference in terms of clinical efficacy (sensory and motor blockade), potency and side effects but more sustained sensory and motor blockade with levobupivacaine.

This study demonstrates that 0.5%3ml isobaric levobupivacaine and 0.5% 3 ml isobaric bupivacaine are equally effective as subarachnoid blockade in lower limb orthopaedic surgery, which requires a sensory blockade of at least T10.

No statistically significant differences were recorded for the sensory blockade onset rate, extent between both local anaesthetics for the onset time, time to maximum spread, motor and sensory blockade duration, which were comparable to results of other studies. However the duration of sensory blockade was prolonged in group B compare to group A but it was not statistically significant. Postoperative VAS and rescue analgesia requirement were similar in both the groups. A similar interval between spinal injection and first voiding in both groups occurred. Group A required postoperative supplemental analgesia before Group B. Both the drugs produce preoperative decrease in MAP and HR, not statistically significant.

Accidental intravenous injection of bupivacaine during attempted epidural anaesthesia in pregnant women caused cardiac arrest. The same event of levobupivacaine caused only transient agitation and the patient recovered fully. Despite some studies providing evidence that levobupivacaine is less cardiotoxic and neurotoxic than bupivacaine^{14,9}, we found no differences between both agents for hemodynamics and incidence of side effects.

At last to summarise, our results show no clinical difference between isobaric levobupivacaine and racemic bupivacaine when administered intrathecally. So bupivacaine remain the cheap and effective choice, although larger group of studies required to further evaluate the efficacy of isobaric levobupivacaine. But it can be concluded that, levobupivacaine seems to be an interesting alternative to bupivacaine for subarachnoid blockade.

6. Conclusions

From the present study, it is concluded that both bupivacaine and levobupivacaine in the dose of 3ml 0.5% in subarachnoid blockade are equally effective and safe with comparable onset, peak, and duration of sensory and motor blockade and post operative analgesia. It can be concluded that levobupivacaine seems to be an interesting alternative to bupivacaine for spinal anesthesia.

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