Journal of Applied Pharmaceutical Research
Volume 11 Issue 3, Year of Publication 2023, Page 18 – 23
DOI: 10.18231/j.joapr.2023.11.3.18.23

Check for updates

Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | ***JOAPR***
www.japtronline.com ***ISSN: 2348 – 0335***

FRACTIONATED DOSE VERSUS BOLUS DOSE OF ISOBARIC INJECTION ROPIVACAINE (0.75%) FOR PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA: A RANDOMIZED, DOUBLE-BLIND STUDY

Anita Pareek[1], Dilip Kochar[1], Richa Kachhawa[1]*, Kritika Bohra[1], Satyaprakash[1], Satvik Kachhawa[2]

Article Information
Received: 31st August 2022
Revised: 28th April 2023
Accepted: 11th June 2023
Published: 31st August 2023

Keywords
Fractionated dose, LSCS, Ropivacaine (0.75%), Spinal Anaesthesia

ABSTRACT

Background: Spinal anaesthesia (SA) using a bolus dose of Ropivacaine (0.75%) is known for its rapid onset but potential chances of hypotension. Administering Ropivacaine (0.75%) in fractions with intervals between the doses, has shown to establish a dense block, prolong analgesia and maintain better hemodynamic stability. This study aimed to compare the efficacy of fractionated and bolus doses of Ropivacaine (0.75%) in patients undergoing elective lower segment caesarean section (LSCS) under spinal anaesthesia. **Methods:** In a randomized, double-blinded trial, sixty patients scheduled for elective LSCS were enrolled and assigned to two groups. Group A received a single bolus spinal anaesthesia using Ropivacaine (0.75%) (2.5ml), while Group B received a fractionated dose approach: two-thirds of the total Ropivacaine (0.75%) dose (1.6ml) initially, followed by one-third dose (0.9ml) after 90 seconds. **Results:** The onset of sensory block (Group A: 3.59±1.31 min, Group B: 4.25±0.63 min) and motor block (Group A: 5.49±2.30 min, Group B: 7.34±11.28 min), as well as the duration of analgesia, were significantly longer in Group B (233.33±16.47 min) compared to Group A (185.17±20.61 min) ($P<0.05$). Hemodynamic stability was superior in Group B, with all patients showing better stability than those in Group A. **Conclusion**: Utilizing a fractionated dose of Ropivacaine (0.75%) in spinal anaesthesia results in an extended duration of analgesia and improved hemodynamic stability compared to a bolus dose approach.

INTRODUCTION

Childbirth is often associated with intense pain, making effective pain management crucial for improving the experience of women in labor. Pain, arising from tissue damage, is a combination of physical and emotional discomfort. For terminally ill patients, adequate pain control is vital for enhancing their quality of life. Bupivacaine, a common local anaesthetic, is frequently used in obstetric analgesia to alleviate

[1]*Department of Anaesthesiology, Sardar Patel Medical College, Bikaner, Rajasthan, India*
[2]*Geetanjali Medical College and Hospitals, Udaipur, Rajasthan, India*

For Correspondence: **richakachhawa1@gmail.com**

labor pain. However, its usage comes with drawbacks, including potential motor impairment and cardiovascular toxicity. These limitations have prompted researchers to explore alternative agents, with Ropivacaine being one such candidate due to its structural similarity to Bupivacaine and Mepivacaine.

Regional anaesthesia techniques, particularly spinal anaesthesia, have gained wide acceptance in both elective and emergency surgeries due to their superior safety profile. Spinal anaesthesia involves administering anaesthetic drugs into the subarachnoid space, rapidly inducing anaesthesia and providing pain relief during and after surgery. The total dose of the local anaesthetic administered is of greater significance than the concentration or volume injected.

Ropivacaine, an S-enantiomer amide local anaesthetic with extended action, offers potential advantages for inducing spinal anaesthesia in caesarean section procedures, due to reduced lower extremity blockage compared to Bupivacaine. Its low lipid solubility allows selective blocking of sensory nerve fibres (Aδ and C fibres) while sparing those controlling motor function (Aß fibres) [1]. This property contributes to the enhanced safety profile of Ropivacaine over Bupivacaine, resulting in reduced central nervous system and cardiovascular toxicity risks [2]. Research by Khaw et al. [3] demonstrated that an effective and safe dose of intrathecal Ropivacaine for achieving spinal block during caesarean section falls between 16.7 and 26.8 mg. Administering a bolus dose of local anaesthetic agent in spinal anaesthesia can lead to significant hypotension. Alternatively, utilizing a fractionated dose approach, where two-thirds of the total calculated dose is initially administered, followed by the remaining one-third dose after a 90-second interval, can achieve sufficient spinal anaesthesia while maintaining stable hemodynamics. However, there is a dearth of evidence comparing these techniques in pregnant patients [4].

Consequently, we designed a comparative study to evaluate the characteristics of the block and the hemodynamic stability associated with the fractionated dose compared to the bolus dose in spinal anaesthesia for elective lower segment caesarean section patients.

METHODOLOGY

The study employed a rigorous and validated prospective, randomized, double-blind, parallel-group, comparative design, which obtained ethical committee approval. Prior to enrolment, written informed consent was obtained from both the mother and her relatives, with exclusion criteria applied.

Inclusion criteria: Parturient with ASA Grade II classification, aged 18-35 years, full-term pregnancy, and live foetus.
Exclusion criteria: Patients who declined participation, exhibited allergies to study drugs, had coagulation defects, local site infections, elevated intracranial pressure, body mass index (BMI) below 20 or above 30, or severe hypovolemia.

The primary objective was to assess and compare the onset, duration, and quality of sensory and motor blocks, as well as postoperative analgesia duration and analgesic consumption within the first 8 hours. The secondary objective involved observing perioperative hemodynamic changes, side effects and complications. To ensure unbiased allocation, patients were randomly divided into two groups of 30 using computer-generated sequences, with concealed allocation through sealed opaque envelopes. An anaesthesiologist not involved in the study, prepared the study drug. Group A received a bolus dose of 2.5ml isobaric Ropivacaine 0.75%, while Group B received a fractionated dose of 1.6ml (12mg) initially followed by 0.9ml after 90 seconds.

Table 1: Allocation of groups based on study drugs

Groups	Drugs	No. of patients
A	Inj. Ropivacaine (0.75%) bolus 2.5 ml	30
B	Fractionated dose of Inj. Ropivacaine (0.75%) initially 2/3rd of the total dose i.e., 1.6ml(12mg) followed by one third dose after 90 sec i.e.,0.9 ml.	30

Prior to surgery, a comprehensive clinical evaluation was conducted on the parturient, encompassing history-taking, a general physical examination and systemic assessment. For all female participants, age, weight, height and baseline vital signs (pulse rate, systolic and diastolic blood pressure, SpO2) were documented. Routine investigations were performed, including haemoglobin levels, platelet count, white blood cell count, bleeding time, clotting time, urine analysis, blood urea, and serum creatinine. The parturients' relatives were briefed about

the anaesthesia technique and the parturients were adhered to the NBM (Nil by Mouth) protocol in accordance with ASA fasting guidelines.

Subsequently, the patients were transported to the operating room (OR), where a multi-parameter monitor was attached to continuously monitor baseline heart rate (HR), blood pressure (BP), and oxygen saturation (SpO2) throughout the procedure. An intravenous line was established using a 22G/24G intravenous (IV) cannula, and injection Ringer lactate solution was infused at a rate of 10ml/kg. The patient was positioned in a sitting posture, and a lumbar puncture was performed at the L3-L4 intervertebral space using a 25G Quincke's cutting spinal needle. After confirming the free flow of cerebrospinal fluid, the predetermined quantity of the study drug was intrathecally administered. Group A participants received a single bolus dose of 2.5 ml Ropivacaine, while Group B participants received a fractionated dose of Ropivacaine. This fractionated dose approach involved initially administering two-thirds of the calculated dose (1.6ml), followed by the remaining one-third dose (0.9ml) after a 90-second interval, both at a rate of 0.2ml/sec. After the initial two-third dose, we kept the syringe attached to the spinal needle for 90 seconds, after which the remaining one-third dose was administered. To prevent observer bias, Group A patients remained in a sitting position for 90 seconds following the completion of the subarachnoid injection. Both groups were then turned into a supine position with a wedge under the right hip. Oxygen supplementation was provided via a face mask at a rate of 4L/min. Sensory and motor block characteristics were evaluated at 5-minute interval and every 30 minutes postoperatively until the sensory and motor parameters returned to normal. Sensory block level was assessed using the pinprick method and motor block was assessed using the Modified Bromage Scale. Successful surgical anaesthesia was defined as achieving sensory block level at or above the T10 dermatome and near complete motor block (Bromage 3). Postoperatively, patients were transferred to the recovery room for ongoing monitoring. The Visual Analog Scale (VAS) score was assessed at 30-minute interval for the first 2 hours and then hourly for up to 6 hours. Intravascular injection of Paracetamol (15 mg/kg) was used as a rescue analgesic.

STATISTICAL ANALYSIS

A sample size of 16 cases in each group was determined to achieve 80% study power and with a 5% alpha error. Considering an expected dropout rate of approximately 40%, the total sample size was calculated to 25 cases for the current study, which we rounded off to 30. Statistical analysis was carried out using Microsoft Excel for data recording. Group comparisons were performed using t-test/Mann–Whitney U test for normally/ non-normally distributed continuous data, respectively. Chi-square test was used for categorical variables. Statistical package for Social Sciences (SPSS) version 23 was used for analysis. $P<0.05$ was taken as the cut-off for statistical significance.

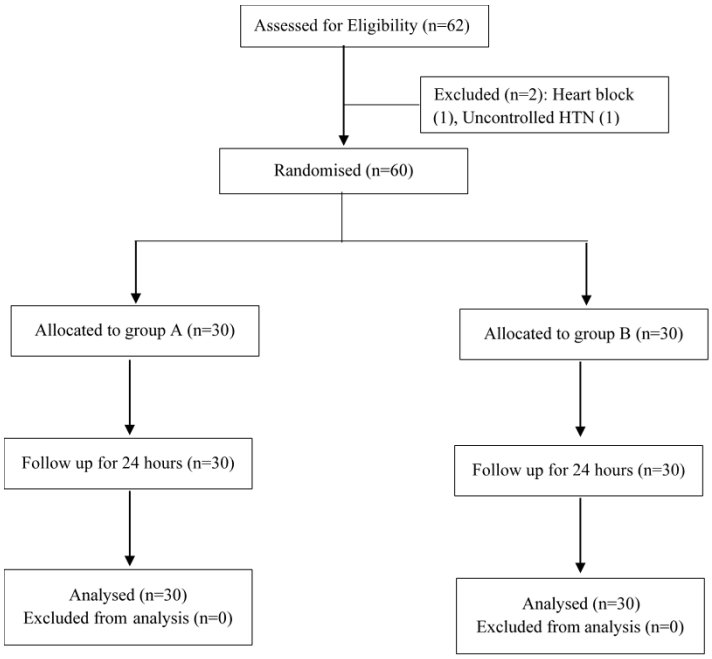

Fig 1: CONSORT chart of the patients recruited and analysed

RESULTS

In our investigation, we undertook a comparison of demographic traits, sensory and motor block characteristics and hemodynamic parameters across two groups of patients subjected to regional anaesthesia. Our analysis revealed that age, weight and height exhibited similar distributions in both groups, as shown in Table 2.

Table 2: Association between demographic parameters

Parameters	Group		p value
	A (n= 30)	B (n= 30)	
Age (Years)	26.53± 4.26	26.43±2.73	0.914
Weight (Kg)	62.03±2.94	62.3±3.07	0.729
Height (cm)	156.86±6.77	158.53±4.79	0.275

Hemodynamic parameters showed similarity across both the groups. Following spinal administration, the mean blood pressure experienced a decline in both groups, with a more

pronounced reduction observed in group A. The disparity in mean blood pressure between the two groups was statistically significant at T15, while it remained insignificant from T5 to T45, as illustrated in Figure 2.

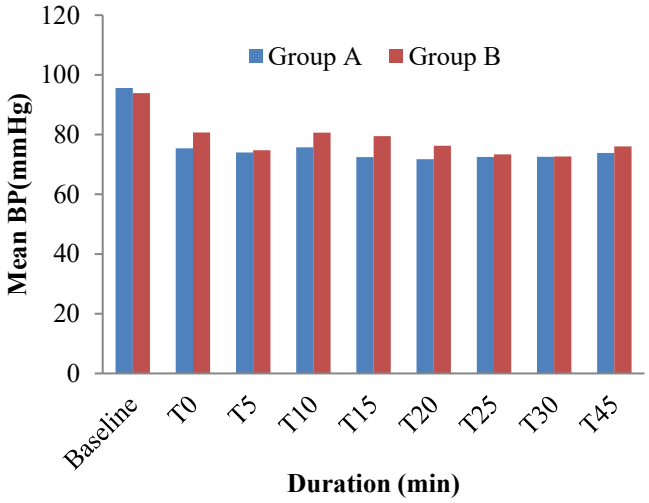

Fig 2: Distribution of cases in both the groups according to mean BP (mmHg)

The mean duration for the onset of sensory block (in minutes), the mean time to reach maximum sensory block (in minutes), and the duration of effective analgesia (in minutes) exhibited statistical significance ($p<0.05$), with higher values observed for the fractionated dose group. In terms of the mean duration of motor block (in minutes), group A displayed a value of 155.0±22.05, whereas group B had a value of 193.67±15.42. Additionally, the duration of two-segment regression (in minutes) was 131.07±25.42 in group A and 176.0±21.75 in group B, both displaying a highly significant statistical difference ($p<0.0001$), as outlined in Table 3. Figure 4 depicts the distribution of cases in both groups according to Duration of effective analgesia (min.). Mean duration of effective analgesia in group A was 185.17±20.61 mins. whereas 233.33±16.47 mins. in group B and the difference was found statistically highly significant ($p<0.0001$*). In our study, only 1 patient in group A, complained of nausea and vomiting, whereas none of the patients in group B complained of complication.

DISCUSSION

The rising prevalence of caesarean section deliveries has led to frequent occurrences of maternal hypotension and excessive spinal blockade following spinal anaesthesia using unadjusted doses of local anaesthetics. Preserving normal blood pressure is pivotal for improving neonatal outcomes. Administering local anaesthetics in fractions with intervals ensures, a dense block with stable hemodynamics and extends the duration of analgesia. Numerous studies support the analgesic efficacy of fractionated local anaesthetic doses for spinal anaesthesia. Ropivacaine's popularity is increasing due to its reduced cardiac toxicity and prolonged action compared to Bupivacaine. As a long-acting local anaesthetic with lower toxicity and fewer side effects, Ropivacaine holds good position. However, studies comparing fractionated and bolus doses of Ropivacaine as spinal anaesthetic agent are scarce. This study aimed to compare the fractionated dose of Ropivacaine (0.75%) with the conventional bolus dose for elective caesarean sections. Given the absence of comparative studies on isobaric Ropivacaine, reference articles utilizing Bupivacaine were employed for comparison, yielding similar findings. For instance, a study by Jigisha et al [4]. compared the fractionated and bolus doses in elective caesarean section spinal anaesthesia, revealing that the fractionated dose produced stable hemodynamics, prolonged analgesia and a dense block.

Table 3: Comparison of block characteristics between the two groups

Parameters	Group		P value
	A (n= 30)	B (n= 30)	
Sensory Block: Onset (minutes)***	3.59±1.31	4.25± 0.63	0.016[1]
Time to Peak Sensory Block (minutes)	5.10±0.20	5.07± 0.25	0.675[1]
Time to maximum sensory block (minutes)***	6.53±2.15	7.87± 0.87	0.002
Sensory Block: Duration of Block (minutes)***	91.38±17.81	75.12±8.97	<0.001[1]
Time to 2-segment regression (minutes)***	131.07± 25.42	176.00± 21.75	0.0001[3]
Duration of effective analgesia (minutes)***	185.17± 20.61	233.33± 16.47	0.001[4]
Motor Block: Onset (minutes)	5.49±2.30	7.34±11.28	0.382[1]
Motor Block: Duration of Block (minutes)***	155.0±22.05	193.67± 15.42	0.0001[3]

****Significant at p<0.05,1: Wilcoxon-Mann Whitney U Test,▪2: Chi Squared Test, 3: t-test, 4: Fisher's Exact Test*

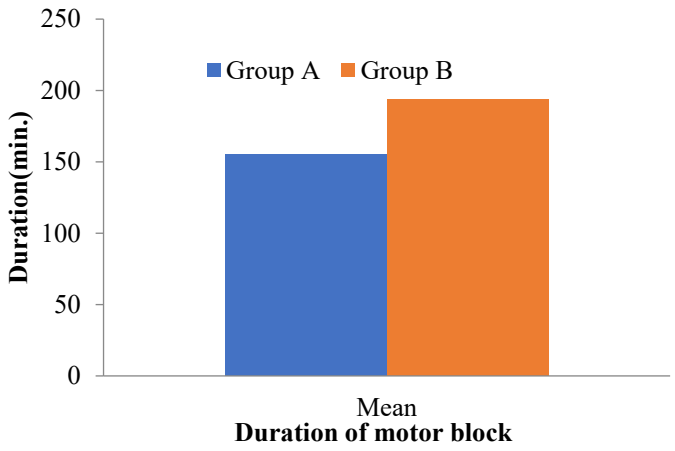

Fig 3: Bar graph depicting duration of motor block in both the groups (min)

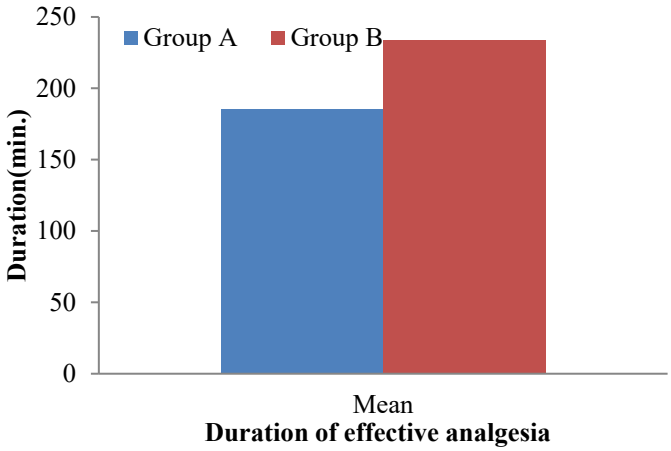

Fig 4: Bar graph depicting duration of effective analgesia in both the groups

Similarly, Favarel et al [5] employed the same technique in elderly patients, administering half of the dose 90 seconds after the initial dose. They reported stable hemodynamics, a dense block and extended analgesia with the fractionated dose. Another study by Fahmy [6], demonstrated that the fractionated dose maintained stable hemodynamics and extended analgesia compared to the bolus dose.

In our investigation, the onset of sensory block was slightly delayed with the fractionated dose compared to the bolus dose (onset in group A: 3.59±1.31 min; group B: 4.25±0.63 min), similar to the study by Mahbuba et al. [7], though their faster onset could be attributed to Bupivacaine usage. Ramasali et al [8] reported a faster sensory block onset with the bolus dose, even with a 60-second interval for the second dose. This contradicts our finding and emphasizes the influence of different local anaesthetics.

In contrast to our study results, Jigisha et al [4] showed an early onset of sensory block in the fractionated group (1.39 ± 0.5 mins) compared to the bolus group (1.5 ± 0.5 mins), which could be attributed to the use of different local anaesthetic. Similar results were seen in Pooya et al [9] study. The duration of sensory blockade was significantly longer in the bolus dose group (91.38±17.81 mins) compared to the fractionated dose group (75.12 ±8.97 mins) (with statistically significant results between the two groups), which is consistent with the findings of Pooya et al [9] study. In our study, the fractionated dose took more time to regress by 2 segments (176.00 ± 21.75 mins) compared to the bolus dose (131.07 ± 25.42 mins), indicating a longer regression time with fractionation. This finding contradicted the study conducted by Ramasali et al [8], which reported a shorter time to 2-segment regression in the fractionated group (93.87±32.81 mins).

Several studies have shown that fractionated doses for spinal anaesthesia result in delayed sensory and motor blockade, which aligns with most of our study results [7,8]. The onset of motor blockade was significantly more prolonged in the fractionated group (group B) compared to the bolus group (group A), which is consistent with the study by Pooya et al [9] but differs from the study by Jigisha et al [4] in terms of the characteristics of motor block onset. They found an early onset of motor block in the fractionated group (4.76±1.07 min) compared to the bolus group (5.867±1.13 min). The fractionated group had a significantly longer duration of analgesia (233.33±16.47 mins) compared to the bolus group (185.17±20.61 mins). Similar results were found in studies by, Jigisha et al [4], Mahbuba et al [7], Ramasali et al [8] and Karinen et al [10].

Throughout the study, mean arterial pressure (MAP) parameters were similar between groups, except at T15, where group B exhibited greater hemodynamic stability. This concurs with studies comparing fractionated and bolus doses of Bupivacaine in elective caesarean sections. Stable hemodynamics were observed in a study with titrated Bupivacaine doses for hip fracture surgery.

CONCLUSION

Spinal anaesthesia with the fractional method offers various advantages including reduced hypotension and bradycardia, longer sensory blockade and a more favourable anesthesia level, along with fewer intra- and post-anaesthesia complications

compared to the classic bolus method. In light of these findings, we deduce that using a fractionated dose of 0.75% Ropivacaine in spinal anaesthesia ensures greater hemodynamic stability and extended analgesia, presenting a preferable approach for elective caesarean sections.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
The study has been carried out under the guidance of Anita Pareek. Dilip Kochar investigated and supervised the whole study. Richa Kachhawa contributed in writing the whole draft and manuscript thereafter. Kritika Bohra curated the data and did analysis. Satyaprakash helped in reviewing of the manuscript. Satvik Kachhawa helped us with accessing resources. All authors approved of the manuscript.

REFERENCES
[1] McClellan KJ, Faulds D. Ropivacaine: an update of its use in regional anaesthesia. *Drugs* **60**, 1065-93 (2000)

[2] Akerman B, Hellberg IB, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiol Scand* **32**, 571-8 (1988)

[3] Khaw KS, Ngan Kee WD, Wong EL, Liu JY, Chung R. Spinal ropivacaine for cesarean section: a dose-finding study. *Anesthesiology* **95**, 1346-50 (2001)

[4] Badheka JP, Oza VP, Vyas A, Baria D, Nehra P, Babu T. Comparison of fractionated dose versus bolus dose injection in spinal anaesthesia for patients undergoing elective caesarean section: A randomised, double-blind study. *Indian J Anaesth* **61**, 55-60 (2017)

[5] Favarel-Garrigues JF, Sztark F, Petitjean ME, Thicoïpé M, Lassié P, Dabadie P. Hemodynamic effects of spinal anesthesia in the elderly: single dose versus titration through a catheter. *Anesth Analg* **82**, 312-6 (1996)

[6] Fahmy NR. Circulatory and anesthetic effects of Bupivacaine for spinal anesthesia fractionated vs bolus administration. *Anesthesiology* **3**, 85 (1996)

[7] Mahbuba S, Chy MMM, Naz S, Begum M, Jahan SS, Sheikh ZA. Comparison of Sensory and Motor Block Outcome of Fractionated Versus Single Bolus Dose Administration of Hyperbaric Bupivacaine in Elective Caesarean Section. *Med. res. chronicles* **8**, 317-324 (2021)

[8] Ramasali MV, Devi VS, Swathi A et al. A Prospective Randomised Double Blind Comparative Study of Bolus versus Fractionated Dose Injection in Spinal Anaesthesia for Pregnant Women undergoing elective Caesarean Section. *Indian J Anesth Analg.* **5(11)**, 184045 (2018)

[9] Derakhshan P, Faiz SHR, Rahimzadeh P, Salehi R, Khaef G. A Comparison of the Effect of Fractionated and Bolus Dose Injection on Spinal Anesthesia for Lower Limb Surgery: A Randomized Clinical Trial. *Anesth Pain Med* **10**, e102228 (2020)

[10] Karinen J, Mäkäräinen L, Alahuhta S, Jouppila R, Jouppila P. Single bolus compared with a fractionated dose injection technique of bupivacaine for extradural Caesarean section: effect on uteroplacental and fetal haemodynamic state. *Br J Anaesth* **77**, 140-4 (1996)