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Fractionated Versus Bolus Intrathecal Dosing of Hyperbaric Levobupivacaine: Implications for Block Characteristics and Hemodynamic Stability in Infraumbilical Surgeries

Dr. Mithai Nauman Hussain,*[1] Dr. Shubham Narayan[1], Dr. Kapil Rastogi[1]

1. Department of Anaesthesiology, Integral Institute of Medical Sciences and Research, Lucknow, India.

***Corresponding Author**

Dr. Mithai Nauman Hussain, (Junior Resident), Department of Anaesthesiology, Integral Institute of Medical Sciences and Research, Lucknow, India.

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ABSTRACT:

Spinal anaesthesia is widely employed for infra-umbilical surgeries because it provides rapid, dense sensory and motor blockade while avoiding airway manipulation. However, conventional bolus intrathecal injection of local anaesthetics is frequently associated with abrupt sympathetic blockade, resulting in hypotension and bradycardia. Fractionated or incremental intrathecal dosing has emerged as a potential strategy to modulate block spread and improve haemodynamic stability without compromising anaesthetic efficacy. Levobupivacaine, the S-enantiomer of bupivacaine, offers comparable anaesthetic characteristics with a superior safety profile due to reduced cardiotoxicity and neurotoxicity. This review explore evidence comparing fractionated versus bolus intrathecal dosing, with emphasis on hyperbaric levobupivacaine. Pharmacological properties, determinants of intrathecal spread, injection techniques, patient factors, and comparative clinical trials across caesarean, orthopaedic, and other infra-umbilical surgeries are discussed. Available evidence suggests that fractionated dosing reduces vasopressor requirements and haemodynamic instability before vasopressor requirements. Nevertheless, direct comparative data for fractionated hyperbaric levobupivacaine remain limited, highlighting the need for further targeted randomised trials.

Introduction

Spinal (subarachnoid) anaesthesia is widely used for infra umbilical surgeries because it produces a dense sensory and motor blockade with rapid onset, allows awake patients, and avoids airway manipulation [1]. However, abrupt sympathetic blockade can lead to hypotension and bradycardia, particularly when large doses of local anaesthetic are administered as a single bolus. Adjusting how intrathecal local anaesthetics are delivered (e.g., bolus versus fractionated doses) has been proposed as a strategy to modulate the spread and hemodynamic effects while maintaining adequate anaesthesia [2,3]. Levobupivacaine, the S enantiomer of bupivacaine, is increasingly used because it produces similar anaesthetic characteristics with reduced cardiotoxicity and neurotoxicity compared with the racemate [4–6].

Stereochemistry and potency

Levobupivacaine is the pure S(−) enantiomer of bupivacaine. The racemic mixture contains S and R isomers, with the R isomer having higher cardiotoxicity and central nervous system toxicity. By eliminating the R isomer, levobupivacaine retains comparable potency but displays lower affinity for myocardial sodium channels, resulting in less myocardial depression and fewer electrocardiographic changes [7]. Randomised clinical trials comparing intrathecal levobupivacaine and racemic bupivacaine found similar onset and duration of sensory and motor block with levobupivacaine but significantly reduced cardiotoxicity [8]. The S isomer has a higher lethal dose and greater protein binding, further increasing its safety margin.

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Baricity and formulations

Baricity—the ratio of solution density to cerebrospinal fluid (CSF) density—determines how a solution spreads in the intrathecal space. Hyperbaric solutions have greater density due to added dextrose and sink within CSF; isobaric solutions have similar density and remain relatively static [9]. Hyperbaric levobupivacaine is prepared by adding dextrose, producing more predictable cephalad spread than isobaric preparations. A double blind trial comparing 0.5 % hyperbaric levobupivacaine (2.52 mL plus 0.48 mL dextrose 8 %) with isobaric levobupivacaine (3 mL plus 0.48 mL saline) in infra umbilical surgeries found hyperbaric levobupivacaine produced faster onset of sensory (7.25 ± 1.68 min vs 11.00 ± 1.747 min), higher maximum block level (≥ T8 in 90 % vs 70 %), and shorter overall duration [10]. This suggests hyperbaric levobupivacaine is better suited for short procedures requiring reliable cephalad spread.

Comparison with other local anaesthetics

Levobupivacaine's potency lies between bupivacaine and ropivacaine. A trial comparing levobupivacaine and ropivacaine for caesarean section found fractionated ropivacaine produced longer analgesia and better hemodynamic stability than bolus dosing, highlighting that dosing strategy influences block characteristics across different agents [11].

Determinants of Intrathecal Drug Spread

The level and duration of sensory and motor block are influenced by solution characteristics, injection technique and patient factors. Understanding these determinants helps contextualise how fractionated dosing might modulate intrathecal spread.

Solution characteristics

Baricity and volume: The density of the solution relative to CSF dictates gravitational movement. Hyperbaric solutions, by virtue of added dextrose, sink and spread along dependent areas when the patient is positioned accordingly, enabling more predictable block heights. Volume and dose also correlate with cephalad spread and block duration; larger volumes produce higher sensory levels and longer duration [9]. The predictive model by Huang et al. derived from 401 adults receiving hyperbaric bupivacaine found that higher doses were associated with higher peak sensory levels, while taller patients and male sex predicted lower block heights [12].

Temperature and viscosity: Warming intrathecal solutions to body temperature reduces viscosity and may accelerate spread. A 2024 randomised double blind trial demonstrated that warming hyperbaric bupivacaine reduced the median effective dose for achieving T6 sensory block in caesarean section from 8.1 mg at 24 °C to 6.7 mg at 37 °C. The study emphasised that warming also shortened onset time, reinforcing temperature as a modifiable determinant [13].

Adjuvants: Opioids and vasoconstrictors influence block quality without significantly altering spread. Lipophilic intrathecal opioids like fentanyl provide rapid analgesia and allow reduction of local anaesthetic dose; hydrophilic opioids like morphine offer prolonged analgesia but risk delayed respiratory depression [14]. Epinephrine or phenylephrine may prolong block by reducing vascular absorption but have minimal impact on initial spread [15,16].

Injection technique

Speed of injection: A prospective randomised study injected 3.2 mL heavy bupivacaine either over 15 s (fast) or 60 s (slow). Faster injection achieved T10 sensory block sooner but required more vasopressors due to greater sympathetic blockade [17]. Slower injection produced comparable block heights but improved hemodynamic stability. These findings support slower or fractionated dosing to mitigate hypotension.

Fractionated dosing: Incremental injection of the same total dose in two or more aliquots separated by a short interval aims to modulate the rate of sympathetic blockade. Pilot studies using heavy bupivacaine suggested that administering two thirds of the dose followed by the remainder after 90 s reduces the sudden increase in sympathetic blockade [18]. This technique is hypothesised to allow some dispersal of the first aliquot before the remaining dose is added, leading to more gradual block establishment and improved hemodynamics.

Patient factors

Age, height, weight, gender and pregnancy all influence intrathecal spread. Higher intra abdominal pressure in pregnancy increases cephalad spread and predisposes to hypotension. Shorter patients achieve higher sensory levels than taller patients receiving equivalent doses [12]. Elderly patients have reduced lumbosacral CSF volume and may experience higher blocks from the same dose

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[9]. Clinicians should account for these factors when choosing dose and injection strategy.

Concept and Rationale of Fractionated Intrathecal Dosing

The fractionated or incremental injection technique divides the total intrathecal local anaesthetic dose into two or more portions separated by a brief interval (e.g., 45–90 s). The rationale is to slow the rate of sympathetic block onset, reducing the incidence and severity of hypotension without compromising the desired level of anaesthesia. By allowing the first aliquot to partially fixate, the second aliquot is less likely to produce excessive cephalad spread.

Early studies using bupivacaine for caesarean section found that fractionated dosing provided hemodynamic stability. Badheka et al. randomised parturients to receive 8 mg heavy bupivacaine with fentanyl either as a single bolus or fractionated (two thirds then one third after 90 s); the fractionated group had significantly fewer vasopressor requirements (5 vs 14 patients) and longer duration of sensory and motor block. The authors hypothesised that the incremental injection produced gradual sympathectomy and improved blood flow to the uterus [18].

Subsequent trials in lower limb orthopaedic surgeries have replicated these findings. A 2020 double blind trial in 70 patients compared a bolus of 15 mg heavy bupivacaine with fentanyl versus fractionated injection (half dose followed by half after 45 s). The fractionated group had longer sensory block duration, lower maximum sensory level and fewer episodes of hypotension [19]. Similarly, another study in elderly patients reported improved hemodynamic stability and reduced vasopressor requirements with fractionated dosing [20]. These results justify exploring the technique with levobupivacaine.

Bolus Intrathecal Injection: Advantages and Limitations

The conventional bolus injection delivers the entire local anaesthetic dose at once, ensuring rapid establishment of a dense sensory and motor block. Clinically, this is simple and time efficient. However, a sudden and high level of sympathetic block often leads to hypotension, bradycardia and nausea. In parturients, spinal induced hypotension occurs in 70–80 % of caesarean sections. Phenylephrine is currently recommended as the first line vasopressor to treat such hypotension because ephedrine is associated with higher risk of fetal acidosis; however, phenylephrine may cause reflex bradycardia and reduced cardiac output [21]. Avoiding large bolus induced sympathectomy would reduce reliance on vasopressors.

Another limitation of bolus dosing is unpredictability of block height in patients with extreme height or weight. The predictive model by Huang et al. demonstrates that fixed bolus volumes may produce variable block heights, especially among females and shorter individuals [12]. Bolus injection also offers limited control over duration; while addition of adjuvants such as morphine or clonidine can prolong analgesia, they do not mitigate initial hemodynamic changes [14].

Comparative Evidence: Fractionated Versus Bolus Dosing

Evidence in caesarean section

Several randomised trials have compared fractionated versus bolus dosing of hyperbaric bupivacaine or levobupivacaine in parturients. Badheka et al.'s 2017 trial mentioned above is among the earliest; fractionated dosing reduced vasopressor use and prolonged analgesia [18]. A 2020 study similarly demonstrated improved hemodynamic stability with fractionation [20]. More recently, a 2024 trial in 60 women undergoing elective caesarean section randomised patients to receive 9 mg hyperbaric bupivacaine with fentanyl either as a single bolus or fractionated (1.6 mL, then 0.6 mL after 90 s). The fractionated group showed faster onset of sensory and motor block, longer duration of analgesia and smaller decreases in systolic and diastolic blood pressure [22]. These consistent findings across multiple trials support fractionated dosing as a means to reduce hypotension during caesarean delivery.

While most studies used bupivacaine, evidence specific to levobupivacaine is emerging. A 2023 randomised study in infra umbilical surgeries compared isobaric levobupivacaine (3 mL of 0.5 %) with hyperbaric bupivacaine. Levobupivacaine produced slower onset but less pronounced hemodynamic changes. Combined with the known lower toxicity of levobupivacaine, fractionated hyperbaric levobupivacaine could further enhance safety; however, dedicated comparative trials remain limited [19].

Evidence in orthopaedic and general surgeries

Fractionated dosing has been studied in lower limb orthopaedic surgery. The 2020 double blind trial

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described earlier found that fractionation resulted in longer sensory block and fewer complications [20]. Another 2023 prospective study evaluated heavy bupivacaine in elderly patients undergoing hip fracture surgery; the fractionated group had better hemodynamic stability and lower vasopressor needs [11]. Additionally, a randomised comparison of fractionated versus bolus ropivacaine in caesarean section showed the fractionated group experienced significantly longer analgesia and improved hemodynamic stability. These results indicate that benefits of fractionated dosing extend beyond a single drug and procedure.

Comparative data on hyperbaric levobupivacaine

Direct evidence comparing fractionated and bolus hyperbaric levobupivacaine is sparse. The majority of trials use bupivacaine; however, extrapolating from levobupivacaine's pharmacology and existing fractionated bupivacaine studies provides rational basis. Hyperbaric levobupivacaine offers faster onset and higher block level than plain levobupivacaine [10]. Given that fractionated dosing slows onset and lowers maximum block level when using heavy bupivacaine, the combination might achieve a desirable intermediate effect—adequate block height with minimal hypotension [20]. Nevertheless, prospective trials directly comparing fractionated hyperbaric levobupivacaine to bolus injection are needed.

Hemodynamic Implications and Management

Hypotension following spinal anaesthesia results from blockade of sympathetic efferent nerves causing vasodilation and decreased venous return. In pregnant women, inferior vena cava compression and aortocaval avoidance further reduce venous return. Clinical management includes volume pre loading or co loading with crystalloids/colloids and prophylactic or reactive vasopressor administration. While ephedrine used to be the first line vasopressor, its association with fetal acidosis has led to phenylephrine becoming the agent of choice [21]. Norepinephrine, offering mild β agonist effects that maintain heart rate and cardiac output, is gaining popularity but awaits definitive evidence.

Fractionated dosing may mitigate hypotension by distributing sympathetic blockade over time. Studies consistently report lower vasopressor requirements with fractionated injection compared with bolus dosing [19,20]. In the 2024 study with caesarean patients, fractionated dosing resulted in less reduction in mean arterial pressure and fewer episodes of nausea and vomiting [22]. However, fractionated dosing cannot completely eliminate hypotension; clinicians should still prepare vasopressors and monitor hemodynamics closely. The effect of fractionation must be balanced against potential prolongation of onset, which may delay surgical start time.

Surgical Context: Infra umbilical Procedures

Infra umbilical surgeries encompass caesarean section, lower limb orthopaedic surgery, urologic procedures, gynaecologic surgery and hernia repair. Subarachnoid block is ideal for these operations because it provides adequate anaesthesia and profound muscle relaxation while avoiding general anaesthetic risks. The required block level varies; caesarean section typically demands sensory blockade up to T4, whereas lower limb surgery may suffice with T10–T12. Fractionated dosing may be particularly beneficial for procedures requiring only lower thoracic block because it may reduce cephalad spread and limit hypotension.

Trials comparing local anaesthetics for various infra umbilical surgeries offer additional insight. The 2016 trial comparing 0.5 % bupivacaine with levobupivacaine in inguinal hernia surgery found levobupivacaine had slower onset but similar anesthetic success and hemodynamic parameters [23]. The authors noted levobupivacaine is underutilised despite its safety advantages. Another trial comparing levobupivacaine with buprenorphine to bupivacaine with buprenorphine for lower limb surgeries reported similar onset but less fall in heart rate and blood pressure in the levobupivacaine group [24]. These findings suggest levobupivacaine may provide a safer alternative for infra umbilical procedures, and fractionated dosing could further enhance hemodynamic stability.

Practical Considerations and Technique Standardisation

When implementing fractionated intrathecal dosing, several technical aspects must be considered:

1. **Dose and volume:** The total dose should be identical to that used in conventional bolus injection, but administered in increments (commonly two thirds and one third). For hyperbaric levobupivacaine 0.5 %, a total dose of 12–15 mg is typical for lower limb surgery, whereas 8–10 mg suffices for caesarean section

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when combined with opioids. Optimal dosing should be tailored to patient size and surgical requirements using predictive factors (height, weight, sex, age) [12].

2. **Timing of aliquots:** Most trials used intervals of 45–90 s between injections [38]. This interval allows partial fixation of the initial aliquot. Injection through a single spinal needle should be smooth; aspiration before the second aliquot ensures correct intrathecal placement.

3. **Injection speed:** Even within fractionated dosing, slower injection speed may reduce hemodynamic changes. Injecting each aliquot over at least 15–30 s is advisable given evidence that fast injection increases vasopressor requirement [17].

4. **Patient positioning:** Maintaining a neutral or slight head up tilt after injection can limit cephalad spread of hyperbaric solutions. In pregnant patients, left lateral tilt helps avoid aortocaval compression.

5. **Adjuvants:** Combining intrathecal opioids (e.g., fentanyl 10–25 µg) with levobupivacaine enhances analgesia and reduces required local anaesthetic dose[14]. Lipophilic opioids are preferred due to rapid onset and short duration.

6. **Monitoring:** Continuous non invasive blood pressure, heart rate and pulse oximetry monitoring is mandatory. Vasopressors (phenylephrine, norepinephrine) should be readily available. Fluid co loading may mitigate hypotension but should be judicious to avoid fluid overload.

7. **Technique standardisation:** Standardising fractionated dosing protocols across institutions will allow better comparison of outcomes and facilitate meta analyses. Future studies should clearly define aliquot volumes, intervals and adjuvant usage.

Gaps in Evidence and Future Research Directions

Despite growing interest, several knowledge gaps remain:

• **Limited evidence specific to levobupivacaine:** Most fractionated dosing studies used bupivacaine. Only a few trials evaluate levobupivacaine, and none directly compare fractionated versus bolus hyperbaric levobupivacaine. Future randomised controlled trials should specifically examine levobupivacaine dosing strategies in different surgical populations.

• **Variation in fractionation protocols:** Studies use different dose splits (50–50 % vs 66–34 %) and intervals (45–90 s), hindering direct comparison. Standardising these parameters and exploring the optimal fractionation scheme is essential.

• **Long term outcomes:** Most studies report intra operative hemodynamics and early block characteristics. Data on long term outcomes, such as chronic pain, neurologic complications and patient satisfaction, are scarce. Assessing whether fractionated dosing affects these outcomes would be valuable.

• **High risk populations:** Frail elderly patients, obese patients, individuals with cardiac disease and emergent surgeries remain underrepresented. Investigating fractionated dosing in these populations will clarify its safety and efficacy.

• **Economic and time considerations:** Fractionated injection may slightly prolong anaesthesia onset and require more attentive administration. Cost–benefit analyses should assess whether the hemodynamic benefits justify the additional complexity.

Conclusion

Levobupivacaine provides effective spinal anaesthesia with a superior safety profile compared with racemic bupivacaine. Intrathecal fractionated dosing, originally developed to mitigate hypotension from bupivacaine, offers a promising strategy to optimise block characteristics and hemodynamic stability. Evidence from randomised trials in caesarean section and lower-limb surgeries demonstrates that fractionated injection reduces vasopressor requirements, prolongs analgesia and provides more controlled sensory block levels. Although specific data on hyperbaric levobupivacaine are limited, its pharmacologic advantages suggest that fractionated dosing could further enhance safety.

Clinical implementation of fractionated dosing requires consideration of total dose, aliquot volume, injection speed and patient factors. While fractionated dosing

cannot eliminate hypotension, it offers an additional tool for clinicians to individualise spinal anaesthesia. Future research should directly compare fractionated versus bolus hyperbaric levobupivacaine across diverse patient populations, standardise protocols and evaluate long-term outcomes. Adopting evidence-based dosing strategies will improve the safety and efficacy of spinal anaesthesia for infra-umbilical surgeries.

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