Systematic Review and Meta-Analysis

# Intrathecal ropivacaine versus bupivacaine in a non-obstetric population- A meta-analysis and trial sequential analysis

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## ABSTRACT

**Background and Aims:** Intrathecal bupivacaine is used for anaesthesia and analgesia but is associated with hypotension. Ropivacaine is an alternative drug that may have fewer cardiotoxic and neurotoxic events. This meta-analysis investigated whether intrathecal ropivacaine is associated with reduced hypotension as compared to bupivacaine. **Methods:** The meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO). The databases PubMed, Cinahl Plus, Google Scholar, and Scopus were searched, and papers from January 1980 to January 2023 were deemed eligible and filtered using predetermined inclusion and exclusion criteria. The primary outcome was the incidence of hypotension. Secondary outcomes were the duration of sensory block, duration of motor block, incidence of bradycardia, ephedrine usage, and duration of analgesia. Jadad scores were used to evaluate the quality of the papers. RevMan statistical software® utilised inverse variance and a random effect model to calculate the standardised mean difference with 95% confidence intervals for continuous variables and the Mantel–Haenszel test and the random effect model to calculate the odds ratio for dichotomous variables. **Results:** Thirty-three papers, including 2475 patients in total, were included. The Jadad score was between 1 and 5. The incidence of hypotension was significantly higher with intrathecal bupivacaine than with ropivacaine ($P = 0.02$). The duration of sensory block ($P < 0.001$) and motor block ($P < 0.001$) was prolonged with intrathecal bupivacaine. The duration of analgesia favoured intrathecal bupivacaine ($P = 0.003$). **Conclusion:** Intrathecal ropivacaine has a reduced incidence of hypotension and a reduced duration of sensory block compared to bupivacaine.

**Keywords:** Anaesthesia, bupivacaine, cardiotoxic, hypotension, intrathecal, ropivacaine, subarachnoid anaesthesia

## INTRODUCTION

Intrathecal anaesthesia is widely used for perioperative anaesthesia and analgesia in non-obstetric procedures but may be associated with complications. After intrathecal administration, ropivacaine does not exhibit equipotency to bupivacaine. The minimum dose of ropivacaine required to achieve anaesthesia comparable to 8mg of bupivacaine in an obstetric setting is 12mg.[1] Khaw *et al.* determined the median effective dose (ED) 50, ED90, and ED95 to be 16.7, 24.5, and 26.8 mg, respectively.[2] The dose ratio of ropivacaine: bupivacaine showing similar profiles of effects was 3:2, and, at equal doses, anaesthesia was less intense using ropivacaine. Hence, we chose



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ropivacaine 8–15mg and >16mg for comparison against bupivacaine in our meta-analysis.[3]

Bupivacaine is associated with spinal anaesthesia-induced hypotension. The incidence varies from 16% to 33% due to a combination of cardiotoxicity (reduced stroke volume) and a reduction in systemic vascular resistance. Perioperative hypotension has several definitions and is associated with postoperative troponin elevation, renal injury, and mortality.[4,5] Wesselink *et al*.[6] showed organ injury with a mean arterial pressure of <80 mmHg for at least 10 min. This risk increased with further drops in blood pressure. Ropivacaine, an S-enantiomer amide local anaesthetic structurally similar to bupivacaine, offers a distinct nerve block profile with reduced motor nerve blockade compared to bupivacaine. Notably, ropivacaine presents significantly lower cardiotoxicity than bupivacaine.

Studies show that ropivacaine is less cardiotoxic than bupivacaine, potentially resulting in an improved cardiovascular profile and less hypotension.[7] A previous meta-analysis showed no difference in the incidence of hypotension between intrathecal ropivacaine and bupivacaine in the obstetric setting.[8] Jaafarpour *et al*.[9] found no differences in the incidence of hypotension between the two drugs for caesarean section. However, studies examining the non-obstetric setting found a mixed picture.[10-13]

We performed a meta-analysis investigating the incidence of hypotension when using intrathecal bupivacaine compared with intrathecal ropivacaine in a non-obstetric population.

## METHODS

We registered our systematic review under the International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42023458006. The meta-analysis adhered to the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The databases PubMed, Cinahl Plus, Google Scholar, and Scopus were searched to identify randomised controlled trials (RCTs), clinical trials, previous meta-analyses, and systematic reviews comparing the intrathecal use of ropivacaine and bupivacaine in non-obstetric populations. Keywords 'intrathecal', 'ropivacaine', and 'bupivacaine' were used to extract the necessary papers relevant to the research without language restriction from January 1980 till January 2023. Only the abstracts, if written in English, were considered. We manually reviewed the remaining papers, assessing their eligibility based on title and abstract. For those with available full articles, inclusion and exclusion criteria were applied to confirm eligibility. Both ropivacaine and bupivacaine needed to be present in the abstract, with studies focused on comparing the efficacy of the two. Non-obstetric population included orthopaedic, urological, lower limb, and lower abdominal surgery. The inclusion criteria for this subset were defined according to the respective authors' definitions in each of the included studies. Free full texts were preferred, and filters were set to study humans only.

The authors RK, AM, and RB performed the literature search. They scored each study according to the Jadad scale, a validated quality of reporting index for RCTs and assigned a final score. Where there was disagreement, a consensus was reached, including a discussion with a third and fourth author (AB and RM). Data were recorded independently by RK, AM, and RB to avoid transcription errors, with any discrepancies resolved by consensus after revisiting the original articles. AB and RM also double-checked all transcriptions. Data was then entered into the statistical program Review Manager 5.1 (Cochrane Library, Oxford, UK) and re-checked by all authors. A funnel plot and risk-of-bias graph were used to assess bias [Figures 1 and 2].

The exclusion of papers involved abstracts studying unilateral intrathecal anaesthesia because an accurate comparison could not be made between unilateral and

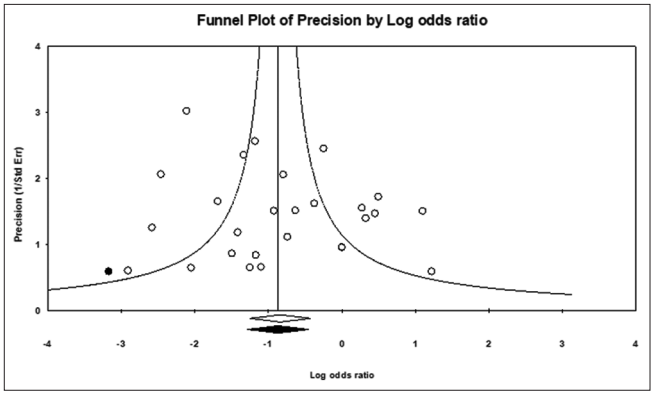



**Figure 1:** Funnel plot and precision plot of publication bias. Std err = standard error


**Figure 2:** Risk of bias

bilateral anaesthesia. Any papers using the median effective dose, minimum local anaesthetic dose, or up-and-down sequential techniques were also excluded as they would not be useful in individually comparing the effects of each agent. Where liposomal additives and levo-isomers were used without the other enantiomer, papers were excluded, as were papers containing case reports of cancer patients. To avoid 'unit of analysis error', the control groups in these studies were divided equally for comparison with the experimental group.[14,15] The primary outcome analysed was the incidence of hypotension, as defined by the respective authors of the included studies. Table 1 demonstrates the characteristics of the included studies. The secondary outcomes were the duration of sensory block and motor block, incidence of bradycardia, use of ephedrine to treat hypotension, and duration of analgesia [Table 2]. All outcomes were adjudged according to the definitions used by the respective authors of the compiled RCTs.

## Statistical analysis

Where possible, meta-analytic techniques using the MetaView software (Review Manager 5.1, Cochrane Library, Oxford, UK) were used to combine the results of the included studies. The odds ratio (OR) and 95% confidence interval (CI) were calculated using a random effects model for dichotomous variables. The results were deemed statistically significant if the 95% CI found did not include 1.0. The risk difference and 95% CI was also calculated for the primary outcome to form a basis for interpretation. Where continuous variables were used, the standardised mean difference (SMD) and 95% CI were calculated using similar random effects modelling. The results were defined as statistically significant, where the 95% CI did not include 0. Clinical variation between studies led to variation in the results. To overcome this, heterogeneity was measured using the $I^2$ statistic. This value describes the level of variation in study findings due to differences in methodology rather than differences due to chance. Numbers needed to treat (NNT) and relative risk reduction (RRR) were calculated as well, where applicable. In cases where data were given as the median with a range or interquartile range (IQR), the mean was estimated as the median and the standard deviation (SD) was approximated to one-quarter of the range of data.[11-13,15,16] Any IQR quoted were compared to represent two SDs.[17]

**Table 1: Characteristics of included studies**

| Authors | Jadad scale | Binding of allocation | Number of Patients | | Concentration (%w/v) | | Dose used (mg) | | Dose Ratio (B: R) | Baricity | Opiate | Volume injected (mL) | | Glucose concentration | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R | B | R | B | R | B | | | | R | B | R | B |
| Atabekoglu and Bozkirli[30] | 2 | Double-blinded | 30 | 30 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Bansal *et al.*[31] | 1 | Unclear | 50 | 50 | 0.5 | 0.5 | 18 | 12 | 1.5 | H | No | 4 | 4 | Not stated | Not stated |
| Bhat *et al.*[32] | 1 | Sealed envelope | 35 | 35 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Boztuğ *et al.*[33] | 1 | Computer-generated mixtures made independently | 45 | 45 | 0.75 | 0.5 | 15 | 7.5 | 2 | I | No | 3 | 3 | U | U |
| Hinojosa-Sánchez *et al.*[34] | 4 | Sealed envelope | 58 | 59 | 0.75 | 0.5 | 15 | 10 | 1.5 | I | No | Not stated | Not stated | U | U |
| Jagtap *et al.*[35] | 4 | Computer randomisation table | 30 | 30 | 0.5 | 0.5 | 15 | 15 | 1 | I | Yes | 3.5 | 3.5 | U | U |
| Kallio *et al.*[14] | 4 | Envelope method | 30 | 30 | 1 | 0.5 | 20 | 10 | 2 | I | No | 2 | 2 | U | U |
| 3rd group (ropivacaine 15 mg) | 4 | | 30 | | 0.75 | | 15 | | 1.5 | I | No | 2 | Not stated | U | |
| Koltka *et al.*[36] | 3 | Unclear | 25 | 25 | 0.75 | 0.5 | 19.5 | 13 | 1.5 | I | Yes (fentanyl 20 µg) | 3 | 3 | U | U |
| Lee[16] | 5 | Computer-generated random codes, sealed envelope | 16 | 17 | 0.5 | 0.5 | 10 | 10 | 1 | I | Yes (fentanyl 15 µg) | 2.3 | 2.3 | U | U |
| Luck[12] | 5 | Unclear | 19 | 20 | 0.5 | 0.5 | 15 | 15 | 1 | H | No | 3 | 3 | 30 mg/ml | 30 mg/ml |
| Malinovsky *et al.*[3] | 1 | Unclear | 50 | 50 | 0.2 | 0.3 | 15 | 10 | 1.5 | I | No | 5 | 5 | U | U |
| Mantouvalou *et al.*[37] | 1 | Sealed envelope | 40d | 40 | 0.75 | 0.5 | 15 | 15 | 1 | I | No | 3 | 3 | U | U |
| Marrett *et al.*[15] | 4 | Sealed envelope | 15 | 17 | 1 | 0.5 | 10 | 10 | 1:1 | I | No | 2 | 2 | U | U |
| | - | - | 16 | - | 1 | - | 10 | - | - | - | Gp 3 sufentanil 2.5 µg | 2 | Not stated | - | - |
| | - | - | 16 | - | 1 | - | 10 | - | - | - | Gp 4 sufentanil 5 µg | 2 | Not stated | - | - |
| McNamee *et al.*[38] | 1 | Unknown | 32 | 34 | 0.5 | 0.5 | 17.5 | 17.5 | 1 | I | No | 3.5 | 3.5 | U | U |
| Mehta *et al.*[39] | 5 | Computer-generated, sealed envelope | 25 | 25 | U | U | 15 | 15 | 1 | I | No | 2 | 2 | U | U |
| Whiteside *et al.*[11] | 4 | Shuffled, sealed envelope | 20 | 20 | 0.5 | 0.5 | 15 | 15 | 1 | H | No | 3 | 3 | 50 mg/ml | 80 mg/ml |
| Athar *et al.*[40] | 5 | Computer-generated randomisation, double-blind | 30 | 30 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Layek *et al.*[13] | 5 | Computer-generated randomisation, double-blind | 37 | 37 | 0.5 | 0.5 | 15 | 15 | 1 | I | Yes, Fentanyl 25 µg | 3 | 3 | U | U |
| Dar *et al.*[10] | 3 | Random allocation | 100 | 100 | 0.5 | 0.5 | 15 | 15 | 1 | H | On request (fentanyl µg/kg) | 3 | 3 | 6.60% | - |
| Ortíz *et al* [41] | 1 | Random allocation | | | 0.75 | 0.5 | 22.5 | 15 | 1.5 | | No | 3 | 3 | - | - |
| Delfino and Vale[42] | 1 | Didn't describe | 15 | 15 | 0.5 | 0.5 | 15 | 15 | 1 | I | No | 3 | 3 | - | - |
| Gautier *et al.*[1] | 5 | Computer-generated list of random numbers, double-blind | 30 | 30 | 0.2 | 0.2 | 8 | 8 | 1 | I | Yes/ | 4 | 4 | U | U |
| Saran *et al.*[43] | 2 | Computer randomised allocation | 50 | 50 | 0.75 | 0.5 | 15 | 10 | 1.5 | I | Yes fentanyl 20 µg | 2 | 2 | U | U |

*Contd...*

**Table 1: Contd...**

| Authors | Jadad scale | Binding of allocation | Number of Patients | | Concentration (%w/v) | | Dose used (mg) | | Dose Ratio (B: R) | Baricity | Opiate | Volume injected (mL) | | Glucose concentration | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | R | B | R | B | R | B | | | | R | B | R | B |
| Kumar *et al.*[44] | 4 | Computer-generated randomisation, double-blind, sealed envelope | 45 | 45 | 0.75 | 0.5 | 15 | 10 | 1.5 | I | No | 2 | 2 | U | U |
| Abhinav and Desai[45] | 1 | Random allocation | 30 | 30 | 0.75 | 0.5 | 26.3 | 17.5 | 1.5 | I | No | 3.5 | 3.5 | U | U |
| Kordcal *et al.*[46] | 4 | Computer-generated, serially numbered opaque sealed envelope (SNOSE), single-blind | 71 | 71 | 0.75 | 0.5 | 15 | 15 | 1 | H | No | 2 | 3 | U | U |
| Prajwal *et al.*[47] | 2 | Open-label road method of randomisation | 50 | 50 | 0.5 | 0.5 | 15 | 15 | 1 | I | Yes, fentanyl 25 µg | 3 | 3.5 | U | U |
| Verma and Mehrotra[48] | 3 | Randomised, double-blind, sealed envelope | 50 | 50 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Adhikari *et al.*[49] | 3 | Sealed envelope method U random allocation | 30 | 30 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Kharat and Deopujari[50] | 4 | Sealed envelope method U random allocation | 35 | 35 | 0.5 | 0.5 | 20 | 20 | 1 | H | No | 4 | 4 | 2 ml of 25% | 2 ml of 25% |
| Surekha *et al.*[51] | 1 | Unknown | 30 | 30 | 0.75 | 0.5 | 16.5 | 11 | 1·5 | I | No | 2.2 | 2.2 | U | U |
| Hazra[52] | 5 | Sealed envelope method U random allocation | 30 | 30 | 0.75 | 0.5 | 22.5 | 15 | 1.5 | I | No | 3 | 3 | U | U |
| Varun *et al.*[53] | 5 | Computer-generated, sealed envelope | 50 | 50 | 0.5 | 0.5 | 15 | 15 | 1 | I | Yes fentanyl 20 µg | 3 | 3 | U | U |

R=Ropivacaine, B=Bupivacaine

Publication bias was represented using a funnel plot [Figure 1]. This graph depicts the effect size on the x-axis and sample size on the y-axis. In this case, the sample size was reported as the log of the standard error on the effect size, where n = number of participants and N = number of trials. If small trials are inappropriately represented, the plot will appear asymmetrical. The risk of bias was represented using a graph [Figure 2]. A sensitivity analysis was also performed to exclude outliers and increase heterogeneity for the primary outcome [Figure 3]. A sub-group analysis was subsequently conducted to determine the effects of differing dosages used for ropivacaine. Meta-regression was performed to ascertain causes for heterogeneity such as dose and volume of local anaesthetic, baricity, types of operation, and Jadad score on the overall outcome. Precision modelling included Duval and Tweedie's 'trim and fill effect' to find missing studies that might impart asymmetry to the funnel plot. These were done for the primary outcome.

We performed a trial sequential analysis (TSA) [Figure 4] by using TSA Viewer (Version 0.9.5.10 Beta, Copenhagen Trial Unit, 2016, Copenhagen, Denmark). The Sidik Jonkman random effects model, less likely to underestimate the heterogeneity between trials, was chosen to calculate the Z-statistic, equal to the meta-analysed intervention effect divided by its standard error. In cumulative meta-analysis, adjusted significance testing has two objectives: (1) to measure and account for the strength of the available evidence and (2) to control for the risk of type-1 and type-2 statistical errors occurring when repeated significance testing on accumulating data is performed.[18] The strength of the available evidence can be considered by determining the required information size (IS) for a conclusive and reliable meta-analysis. It can be derived from the risk of type-1 and type-2 statistical errors, which we set at 5% and 20%, respectively, resulting in a power of 80%.

**Table 2: Secondary outcome measures**

| Variable | Number of studies/participants | Standard mean difference or odds ratio (95% CI) | *P* |
|---|---|---|---|
| Duration of sensory block | 30/2168 | SMD −0.76 (−1.08–−0.45) | <0.001 |
| Duration for motor block | 31/2289 | SMD −1.85 (−2.48–−1.22) | <0.001 |
| Incidence of bradycardia | 28/1996 | OR 0.52 (0.32–0.84) | 0.007 |
| Ephedrine usage | 9/752 | OR 0.47 (0.18–1.22) | 0.120 |
| Duration of analgesia | 7/464 | SMD −0.79(−1.48–−0.09) | 0.030 |

SMD=Standard mean difference, OR=odds ratio

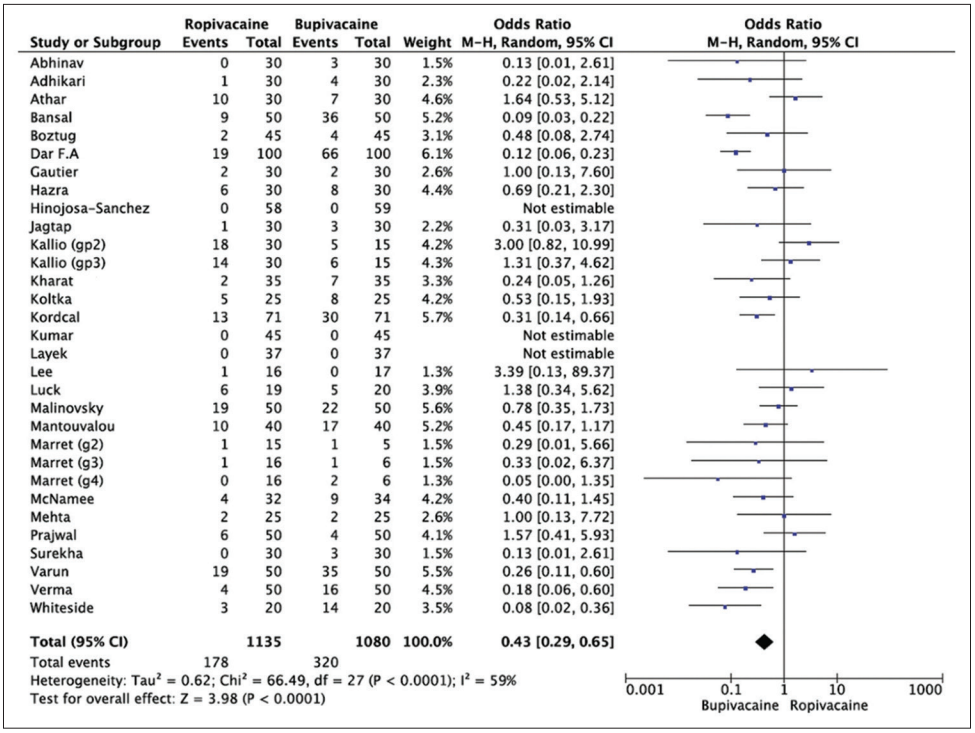



**Figure 3:** Forest plot of incidence of hypotension. MH=Mantel–Haenszel, CI=Confidence Interval, Kallio (gp2)=Ropivacaine 20mg Vs Bupivacaine 10mg, Kallio (gp3)=Ropivacaine 15mg Vs Bupivacaine 10mg, Marret (g2)=no opioid, Marret (g3)=with sufentanil 2.5mg, Marret (g4)=with sufentanil 5μg

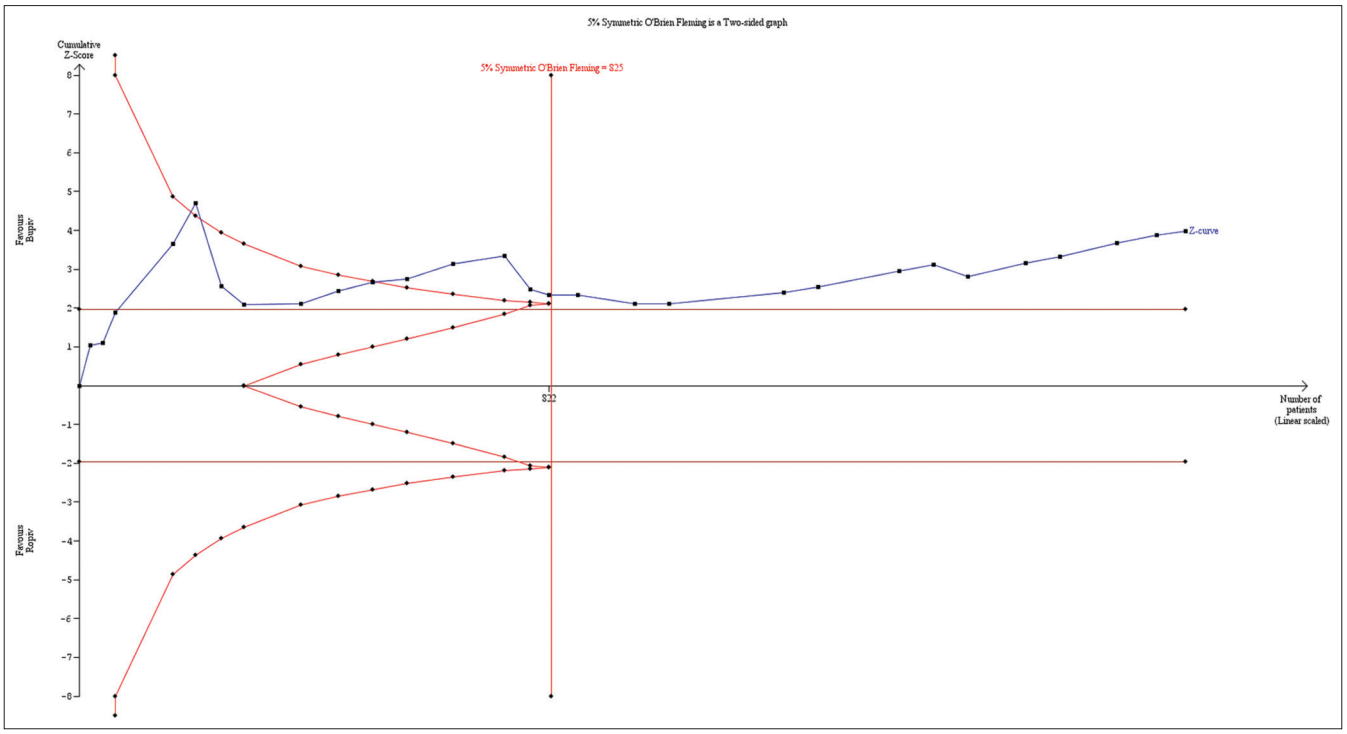



**Figure 4:** Trial Sequential Analysis for overall hypotension. The blue z curve represents the cumulative sum of participants; the vertical red line represents the required information size (IS); the outer inward sloping red coloured lines represent the trial sequential monitoring boundaries; the inner sloping lines signify the futility boundary; the brown upper and lower horizontal lines represent the conventional boundary

## RESULTS

We retrieved 33 studies comprising 2475 patients in total. The Jadad score for quality of reporting was between 1 and 5. Meta-regression did not show any impact on the overall outcome with $P$=0.12 with all covariates considered. No publication bias was observed for the included studies, with Egger's regression coefficient being $P$=0.36. The funnel plot and the precision funnel plot showed no asymmetry [Figure 1]. The 'trim and fill effect' did not show any unaccounted-for studies on the left or the right of the mean using a random or fixed effects model. Figure 5 displays the flow diagram showing the number of included and excluded studies [Figure 5].

### Primary outcome

#### *Incidence of hypotension [Figures 3 and 6]*

Thirty-one studies, including 2215 participants, were included to compare the incidence of hypotension. The incidence of hypotension was higher in the bupivacaine group compared to the ropivacaine group (SMD: 0.43, 95% CI: 0.29–0.65, $P$<0.001, $I^2$ = 59%). Further sub-group analysis was performed to compare the incidence of hypotension and type of operation, including orthopaedic, major limb, arthroscopy, mixed 'author-defined' surgeries (including lower abdominal, limb and gynaecology surgery) and urology. Analysis revealed no significant difference in orthopaedic/major limb/arthroscopy and urological operations ($P$=0.23 and $P$=0.21, respectively). However, a higher incidence of hypotension was found in mixed 'author-defined' surgeries (including lower abdominal, limb and gynaecology surgery), with $P$<0.001. Despite this, the test for sub-group analysis found no significant difference between the type of surgery and the incidence of hypotension ($P$=0.36, $I^2$ = 1%). There were not enough studies using preloading versus co-loading to analyse the hypotension incidence further. As per TSA, there were not enough patients (n = 2769, 7681, and 623) for the hypotension definitions of 25%, 20%, and 30%, respectively, as defined by the authors. Sensitivity analysis excluding the outliers did not alter the $P$ value or the direction of the overall outcome. However, as per TSA [Figure 4], the overall sample size for incidence of hypotension was much greater than the estimated sample size (n = 825).

NNT and RRR: The calculated NNT was 9, and the RRR was 43% in favour of intrathecal ropivacaine in having reduced incidences of hypotension.

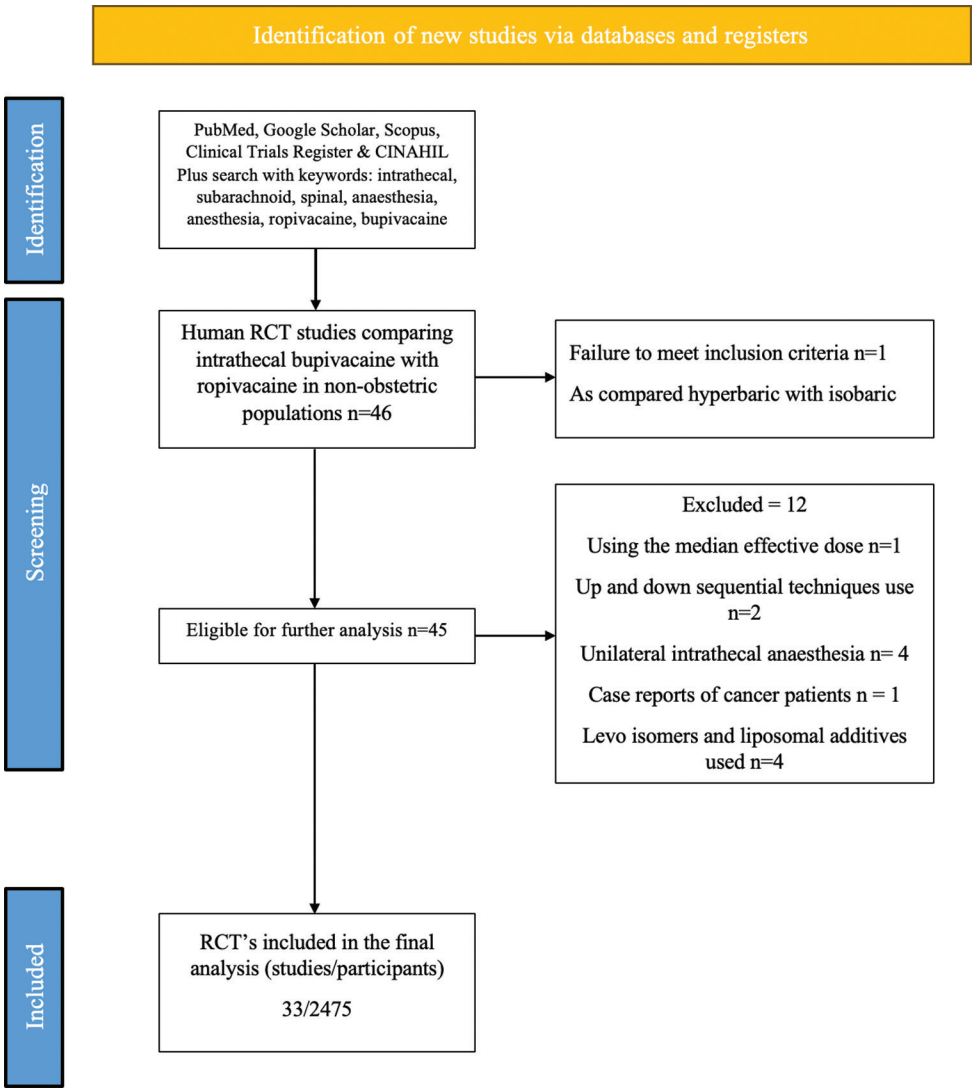



**Figure 5:** Flowchart according to Preferred Reporting Items for Systematic Reviews and Meta Analysis. RCT = Randomised Controlled Trials

### *Duration of sensory block*

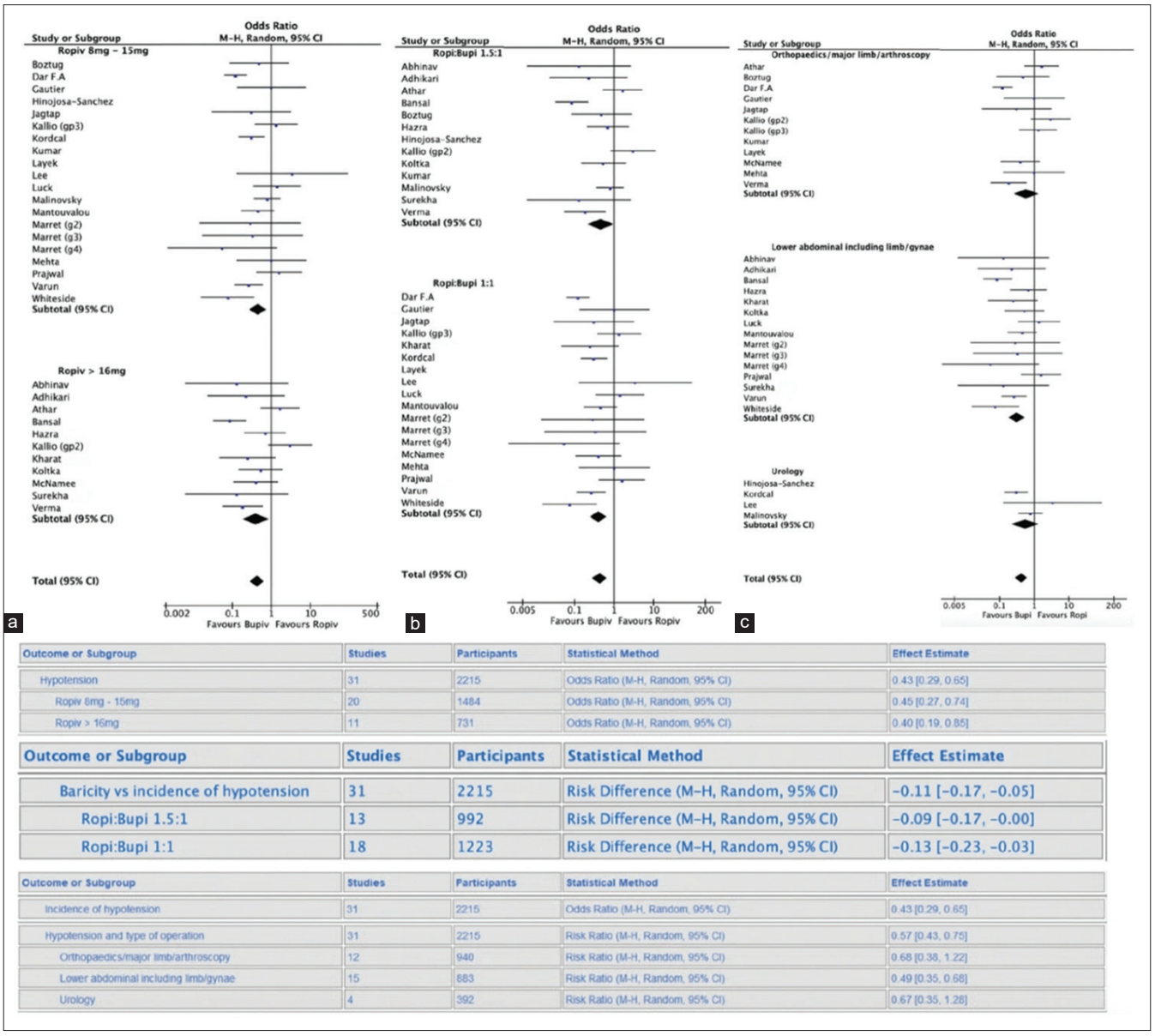
The duration of the sensory block was prolonged in the bupivacaine group compared to the ropivacaine group ($P<0.001$) [Table 2]. The mean duration was approximately 25 min longer for patients receiving intrathecal bupivacaine.

TSA analysis furthermore demonstrated that IS for orthopaedics, major limb arthroscopy (n = 3002) was not attained for it to be significant enough as more RCTs are required to make an informed decision; thus, based on the current evidence, results should be used with caution. On the contrary, for mixed 'author-defined' surgeries (including lower abdominal, lower limb and urology), TSA analysis revealed the IS sample size was reached in both instances at n = 946 and 218, respectively, thereby confirming intrathecal ropivacaine's superiority over bupivacaine under the circumstances.

Further sub-group analysis based on the ratio of baricity showed that the results for a 1:1 ratio were achieved (n=328), thereby proving that the results portend extended duration of sensory block to be more with intrathecal bupivacaine undoubtedly compared to 1.5:1 wherein the sample size fell short of the required IS (n=2581), demonstrating limited evidence to suggest its benefit requiring more RCTs to be conducted. Sensitivity analysis excluding the outliers did not alter the *P* value or the direction of the overall outcome.

### *Duration of motor block*

The duration of the motor block was significantly longer with bupivacaine than with ropivacaine ($P<0.001$) [Table 2]. Sensitivity analysis excluding the outlier did not change the direction of the overall outcome or *P* value, with $P<0.001$ and




| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| Hypotension | 31 | 2215 | Odds Ratio (M-H, Random, 95% CI) | 0.43 [0.29, 0.65] |
| Ropiv 8mg - 15mg | 20 | 1484 | Odds Ratio (M-H, Random, 95% CI) | 0.45 [0.27, 0.74] |
| Ropiv > 16mg | 11 | 731 | Odds Ratio (M-H, Random, 95% CI) | 0.40 [0.19, 0.85] |

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| Baricity vs incidence of hypotension | 31 | 2215 | Risk Difference (M-H, Random, 95% CI) | -0.11 [-0.17, -0.05] |
| Ropi:Bupi 1.5:1 | 13 | 992 | Risk Difference (M-H, Random, 95% CI) | -0.09 [-0.17, -0.00] |
| Ropi:Bupi 1:1 | 18 | 1223 | Risk Difference (M-H, Random, 95% CI) | -0.13 [-0.23, -0.03] |

| Outcome or Subgroup | Studies | Participants | Statistical Method | Effect Estimate |
|---|---|---|---|---|
| Incidence of hypotension | 31 | 2215 | Odds Ratio (M-H, Random, 95% CI) | 0.43 [0.29, 0.65] |
| Hypotension and type of operation | 31 | 2215 | Risk Ratio (M-H, Random, 95% CI) | 0.57 [0.43, 0.75] |
| Orthopaedics/major limb/arthroscopy | 12 | 940 | Risk Ratio (M-H, Random, 95% CI) | 0.68 [0.38, 1.22] |
| Lower abdominal including limb/gynae | 15 | 883 | Risk Ratio (M-H, Random, 95% CI) | 0.49 [0.35, 0.68] |
| Urology | 4 | 392 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.35, 1.28] |

**Figure 6:** Forest plots and effect estimates for sub-groups:(a) Ropivacaine 8–15mg vs ropivacaine >16mg. (b) Ropivacaine:Bupivacaine 1.5:1 vs 1:1. (c) Types of surgery – orthopaedics vs lower abdominal vs urology. MH=Mantel–Haenszel, CI=Confidence Interval, g/gp=group, ropi/ropiv = Ropivacaine, bupi = Bupivacaine, Kallio (gp2)=Ropivacaine 20mg Vs Bupivacaine 10mg, Kallio (gp3)=Ropivacaine 15mg Vs Bupivacaine 10mg, Marret (g2)=no opioid, Marret (g3)=with sufentanil 2.5μg, Marret (g4)=with sufentanil 5μg

$I^2$ = 97%. The mean duration of the motor block for the bupivacaine group was approximately 41 min longer than that for the ropivacaine group. Sub-group analysis was also performed to compare the duration of motor block in ropivacaine 8–15 mg and ropivacaine >16 mg to bupivacaine. The results indicated no significant difference between the two groups ($P$<0.001 for both), and the test for subgroup differences showed a non-significant result ($P$=0.10, $I^2$ = 63.3%). TSA performed for both sub-groups revealed adequately powered sample size to justify the above results.

### *Incidence of bradycardia*

Analysis of the incidence of bradycardia included 28 studies with 1996 patients [Table 2]. Results found a significant difference between bupivacaine and ropivacaine ($P$=0.007, $I^2$ = 35%). Sub-group analysis was performed to compare different doses of ropivacaine (8–15 mg) and ropivacaine >16mg. Results revealed a significant difference at doses between 8 and 15 mg ($P$=0.03). However, no significant difference was found at higher doses (>16 mg), with $P$=0.09. Test for sub-group differences revealed $P$=0.31 and $I^2$ = 2.5%. However, these results for the overall incidence of bradycardia and

the sub-groups should be treated cautiously as the sample size to justify a relative reduction of 41% fell short of the estimated sample size, proving that more well-designed RCTs are required to explain the outcome. Sensitivity analysis excluding the outliers did not alter the *P* value or the direction of the overall outcome.

### *Ephedrine*

There were n/N (studies/participants) = 9/752 with *P*=0.12, demonstrating non-significance [Table 2]. However, on TSA analysis, the estimated IS for the outcome was 1220, which is more than our sample size N=752, justifying that more RCTs are required and that the results from this meta-analysis should be interpreted cautiously. However, the NNT and the RRR were similar in terms of the incidence of hypotension. Sensitivity analysis excluding the outliers did not alter the *P* value or the direction of the overall outcome.

### *Duration of analgesia*

There were 7/464 studies/participants (*P*=0.03) [Table 2]. The mean difference in analgesic duration was approximately 37 min more for the bupivacaine group. However, TSA analysis showed that the IS sample size of 705 participants was not reached. This prompted us to conclude that the results should be interpreted cautiously and that more RCTs are required to justify the benefits conclusively.

## DISCUSSION

The incidence of hypotension was significantly higher with intrathecal bupivacaine than with ropivacaine ($P = 0.02$). The duration of sensory block ($P < 0.001$) and motor block ($P < 0.001$) was prolonged with intrathecal bupivacaine.

Studies have shown conflicting results regarding the evidence for reduced hypotension with intrathecal ropivacaine compared to bupivacaine. Animal studies have shown that bupivacaine results in a greater and more prolonged deleterious change in cardiac index, heart rate, and mean arterial pressure compared to ropivacaine.[19] Sub-group analysis studying the type of surgery and incidence of hypotension revealed a higher incidence in the bupivacaine group with mixed 'author-defined' surgeries (including lower abdominal, limb and gynaecology surgery), compared to the orthopaedic, major limb, arthroscopy and urology sub-group.[6] The reason could be that the required information size (IS) calculated using TSA was reached for the sub-group having mixed 'author-defined' surgeries including lower abdominal and limb/gynaecological procedures (n=324) compared to the orthopaedic/limb/arthroscopy sub-group (n=2414), thereby prompting us to conclude that more focussed RCTs are needed in the latter sub-group to conclude intrathecal ropivacaine's benefits over intrathecal bupivacaine for the latter sub-group.

Preload and lower doses of bupivacaine can reduce the risk of hypotension. However, even low doses of bupivacaine (7.5 mg) resulted in 66% of patients over the age of 70 years developing hypotension.[20] The authors have used varying definitions of hypotension; therefore, a sub-group analysis was not possible. However, when a sample size estimation was performed based on the varying definitions of hypotension, the IS for the different definitions invariably fell short of the required number of patients of 2769, 1073, and 623 for 25%, 20%, and 30% reductions in blood pressure, respectively, as described by the authors to show any impact. This proves that more well-designed and standardised RCTs are required to validate this, and the results for this outcome should be treated with caution. There were not enough studies to analyse the incidence of hypotension based on preloading versus co-loading. Meta-regression performed for variables such as Jadad score, dose, and volume of ropivacaine versus bupivacaine, definitions of hypotension, baricity, and type of operation did not reveal any significance (*P*=0.71).

In addition, intrathecal bupivacaine has a prolonged duration of sensory block compared to intrathecal ropivacaine. Intrathecal bupivacaine causes a more prolonged duration of sensory block for lower abdominal and urological procedures but has not been convincing enough to demonstrate the same benefit in orthopaedic cases. Stienstra acknowledged that the relative potency of ropivacaine to bupivacaine has yet to be fully known as the results of several trials in multiple settings have conflicted.[21] An initial *in vitro* study showed that bupivacaine had a 16% greater depressant effect on motor fibres than an equal dose of ropivacaine; sensory blockade was considered equivalent.[22] However, several clinical studies have shown no equivalent or predictable relationship between ropivacaine and bupivacaine regarding sensory block.[23] The relative potencies have been variable, dependent upon the route of administration and doses used. For example, ropivacaine appears more potent than bupivacaine when given by the

caudal route in children but only half as potent when given intrathecally to volunteers.[24] The reason for this is difficult to explain. The dose-response curves of the two drugs have points of intersection dependent on the doses used or the routes administered.[24] This would explain why trials using different doses of local anaesthetic agents show such varied relative potencies; each trial would only be investigating a small section of the dose-response curve and so conclude a relative potency that cannot be extrapolated to all parts of the curve.

Regarding the duration of motor block, intrathecal ropivacaine has a shorter duration of motor block ($P<0.001$) compared with intrathecal bupivacaine. This was also true for sub-group analysis, proving that the duration of motor block is not dependent on the relative dose of ropivacaine. This may suggest that ropivacaine should be used for shorter procedures to allow for the adoption of the principles of enhanced recovery.[25] One study suggests that early recovery from motor block is part of enhanced recovery, translating to shorter stays.[26]

Our study also refutes the assertion that intrathecal ropivacaine produces a prolonged duration of analgesia compared to intrathecal bupivacaine. However, more studies are needed to conclusively prove it, as the required IS (n=705) was not reached.[27]

Several limitations of this meta-analysis need to be acknowledged. There are methodological flaws with varying Jadad scores regarding allocation to blinding. Nevertheless, meta-regression and Egger's test did not reveal any impact of the Jadad scoring on outcome measures. Despite the definitions of hypotension used by the authors, there was overwhelming evidence to suggest the benefits of intrathecal ropivacaine in mitigating hypotension overall, not considering the subset of types of operations.[10,11,31,46,48,53] This has also been supported by using ephedrine in combating hypotension in terms of similar NNT and RRR, even though the required information size was not reached due to the limited number of available trials. Meta-regression did not demonstrate any impact of the variables on the observed heterogeneity. Different dosages of ropivacaine and bupivacaine were used, and we could not analyse with certainty at which dose one would notice the most definitive effect on the incidence of hypotension. Despite high heterogeneity for the duration of sensory block, meta-regression performed did not find any contributing factors. While there is a statistical significance indicating a 25-minute reduction in mean duration with intrathecal ropivacaine, it remains uncertain whether this reduction holds clinical significance, as patients typically spend a similar amount of time in the post-anaesthetic care unit following their operation.[27] Although there is an RRR of 41% for the incidence of bradycardia in favour of intrathecal ropivacaine, the sample size was not large enough (n = 2801) to enable us to conclude definitively in favour of it. Ropivacaine is more expensive than bupivacaine, but no direct comparison of equivalent doses for intrathecal use has been performed; this expense could easily be offset by facilitating enhanced recovery after surgery principles.[28,29]

## CONCLUSION

This meta-analysis suggests that intrathecal ropivacaine is associated with a lower incidence of hypotension and a shorter duration of motor block than intrathecal bupivacaine but a shorter duration of sensory block. The choice of anaesthetic agent should be tailored to the specific surgical procedure and patient characteristics. Careful consideration should be given to the definition of hypotension when interpreting studies. However, more robust RCTs with standardised definitions of hypotension are needed to convincingly determine the benefits of ropivacaine over bupivacaine when used intrathecally.

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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B, *et al*. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for caesarean section. Br J Anaesth 2003;91:684-9.
2. Khaw KS, Ngan Kee WD, Wong EL, Liu JY, Chung R. Spinal ropivacaine for cesarean section. Anesthesiology 2001;95;1346-50.
3. Malinovsky JM, Charles F, Kick O, Lepage JY, Malinge M, Cozian A, *et al*. Intrathecal anaesthesia: Ropivacaine versus bupivacaine. Anesth Analg 2000;91:1457-60.
4. Van Lier F, Wesdorp FHIM, Liem VGB, Potters JW, Grüne F, Boersma H, *et al*. Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. Br J Anaesth 2018;120:77-8.
5. Khanna AK, Maheshwari K, Mao G, Liu L, Perez-Protto SE, Chodavarapu P, *et al*. Association between mean arterial pressure and acute kidney injury and a composite of myocardial injury and mortality in postoperative critically

ill patients: A retrospective cohort analysis. Crit Care Med 2019;47:910-7.
6. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. Br J Anaesth 2018;121:706-21.
7. Graf BM, Abraham I, Eberbach N, Kunst G, Stowe DF, Martin E, *et al*. Differences in cardiotoxicity of bupivacaine and ropivacaine are the result of physicochemical and stereoselective properties. Anesthesiology 2002;96:1427-34.
8. Malhotra R, Johnstone C, Halpern S, Hunter J, Banerjee A. Duration of motor block with intrathecal ropivacaine versus bupivacaine for caesarean section: A meta-analysis. Int J Obstet Anesth 2016;27:9-16.
9. Jaafarpour M, Vasigh A, Najafi F, Sayadi H, Shafiei E. A comparative study on the effect of intrathecal bupivacaine vs. ropivacaine on maternal and neonatal outcomes after cesarean section: A systematic review and meta-analysis.Anesth Pain Med 2023;13:e134732. doi: 10.5812/aapm-134732.
10. Dar FA, Mushtaq MB, Khan UM. Hyperbaric spinal ropivacaine in lower limb and hip surgery: A comparison with hyperbaric bupivacaine. J Anaesthesiol Clin Pharmacol 2015;31:466-70.
11. Whiteside JB, Burke D, Wildsmith JAW. Comparison of ropivacaine 0.5% (in glucose 5%) with bupivacaine 0.5% (in glucose 8%) for spinal anaesthesia for elective surgery. Br J Anaesth 2003;90:304-8.
12. Luck, JF, Fettes PDW, Wildsmith JAW. Spinal anaesthesia for elective surgery: A comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and Ropivacaine. Br J Anaesth 2008;101:705–710.
13. Layek A, Maitra S, Gozi NK, Bhattacharjee S, Pal S, Sen S, *et al*. Comparison between intrathecal isobaric ropivacaine-fentanyl and bupivacaine-fentanyl in elective infraumbilical orthopedic surgery: A randomized controlled study. J Anaesthesiol Clin Pharmacol 2015;3:542-6.
14. Kallio H, Snall EVT, Kero MP, Rosenburg PH. A comparison of intrathecal plain solutions containing ropivacaine 20 or 15 mg versus bupivacaine 10 mg. AnesthAnalg 2004;99:713-7.
15. Marrett E, Thevenin A, Gentili M, Bonnet F. Comparison of intrathecal bupivacaine and ropivacaine with different doses of sufentanil. Acta Anaesthesiol Scand 2011;55:670-6.
16. Lee YY, Ngan Kee WD, Muchhal K, Chan CK. Randomized double-blind comparison of ropivacaine-fentanyl and bupivacaine-fentanyl for spinal anaesthesia for urological surgery. Acta Anaesthesiol Scand 2005;49:1477–1482.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13. doi: 10.1186/1471-2288-5-13.
18. Shah A, Smith AF. Trial sequential analysis: Adding a new dimension to meta-analysis. Anaesthesia 2020;75:15-20.
19. Melo MDS, Silva WA, Moraes AC, Udelsmann A. Comparison of hemodynamic changes in acute intoxication with intravenous bupivacaine and ropivacaine in swine. Braz J Anesthesiol 2009;59:592-601.
20. Lairez O, Ferre F, Portet N, Marty P, Delmas C, Cognet T, *et al*. Cardiovascular effects of low-dose spinal anaesthesia as a function of age: An observational study using echocardiography. Anaesth Crit Care Pain Med 2015;34:271-6.
21. Stienstra R. The place of ropivacaine in anesthesia. Acta Anaesth Belg 2003;54:141-8.
22. Bader AM, Datta S, Flanagan H, Covino BG. Comparison of bupivacaine-and ropivacaine-induced conduction in blockade in the isolated rabbit vagus nerve. AnesthAnalg 1989;68:724-7.
23. Ivani G, Mereto N, Lampugnani E, Negri PD, Torre M, Mattioli G, *et al*. Ropivacaine in paediatric surgery: Preliminary results. PaediatrAnaesth 1998;8:127-9.
24. Holdcroft A, Thomas TA. Regional anaesthetic techniques. In: Principles and Practice of Obstetric Anaesthesia and Analgesia. Oxford: Blackwell Science: 2000. p. 227-82.
25. Agarwala R, Morrison B. Neuraxial anaesthesia and its role in enhanced recovery after surgery: A narrative review. Dig Med Res 2022;5:20.
26. Moningi S, Patki A, Padhy N, Ramachandran G. Enhanced recovery after surgery: An Anesthesiologist's perspective. J Anaesthesiol Clin Pharmacol 2019;35(Suppl 1):S5-13.
27. Chang J, Fossum S R, Alderson W C, Pedersen M A. 1.7 - PACU Setup and Requirements. Global Reconstructive Surgery. In J. Chang, 2019. Edinburgh: Elsevier. 45–49.
28. Dhalwani N. Ropivacaine versus bupivacaine for spinal anesthesia in elective caesarean deliveries. J Pioneer Med Sci 2012;2:73-4.
29. Dong Y, Zhang Y, Jin C. Comprehensive economic evaluation of enhanced recovery after surgery in hepatectomy. Int J Equity Health 2021;20:245. doi: 10.1186/s12939-021-01583-3.
30. Atabekoglu S, Bozkirli F. Comparison of the clinical effects of intrathecal ropivacaine and bupivacaine in geriatric patients undergoing transurethral resection. Gazi Med J 2007;18:182-5.
31. Bansal DS, Ramdev DB, Narula DP, Bansal DS, Kaur D, Rathi S. Comparative evaluation of intrathecal hyperbaric ropivacaine versus intrathecal hyperbaric bupivacaine in elective lower abdominal and lower limb surgery. IOSR J Dent Med Sci 2015;14:27-31.
32. Bhat S, Himaldev, Upadya M. Comparison of efficacy and safety of ropivacaine with bupivacaine for intrathecal anesthesia for lower abdominal and lower limb surgeries. Anesth Essays Res 2013;7:381-5.
33. Boztuğ N, Bigat Z, Karsli B, Saykal N, Ertok E. Comparison of ropivacaine and bupivacaine for intrathecal anesthesia during outpatient arthroscopic surgery. J Clin Anesth 2006;18:521-5.
34. Hinojosa-Sánchez O, Alamilla-Beltrán I, Han-Alonso R, Solano-Moreno H, Alvarez-Villaseñor AS, Ramírez-Contreras JP, *et al*. Subarachnoid blockade with ropivacaine versus bupivacaine in urologic and orthopedic surgery. Rev Med Inst Mex Seguro Soc 2009;47:539-44.
35. Jagtap S, Chhabra A, Dawoodi S, Jain A. Comparison of intrathecal ropivacaine-fentanyl and bupivacaine-fentanyl for major lower limb orthopaedic surgery: A randomised double-blind study. Indian J Anaesth 2014;58:442-6.
36. Koltka K, Uludag E, Senturk M, Yavru A, Karadeniz M, Sengul T, *et al*. Comparison of equipotent doses of ropivacaine-fentanyl and bupivacaine-fentanyl in spinal anaesthesia for lower abdominal surgery. Anaesth Intensive Care 2009;37:923-8.
37. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anesthesia: Comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. Acta Anaesthesiol Belg 2008;59:65-71.
38. McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: Comparison of plain ropivacaine 5 mg ml-1 with bupivacaine 5 mg ml-1 for major orthopaedic surgery. Br J Anaesth 2002;89:702-6.
39. Mehta A, Gupta V, Wakhloo R, Gupta N, Gupta A, Bakshi R, *et al*. Comparative evaluation of intrathecal administration of newer local anaesthetic agents ropivacaine and levobupivacaine with bupivacaine in patients undergoing lower limb surgery. Internet J Anesthesiol 2007;17:1.
40. Athar M, Ahmed SM, Ali S, Doley K, Varshney A, Siddiqi MMH. Levobupivacaine or ropivacaine: A randomised double blind controlled trial using equipotent doses in spinal anaesthesia. Colomb J Anesthesiol 2016;44:97-104.
41. Ortíz HC, Guzmán L, Jiménez A, Becerril G, Marañón R, Segura RT. Comparison of 0.75% spinal ropivacaine with 0.5% spinal ropivacaine for orthopedic surgery of lower limbs. Rev Mex Anestesiol 2002;25:252-6.
42. Delfino J, Vale NB. Spinal anesthesia with 0.5% isobaric ropivacaine or levobupivacaine for lower limb surgeries. Rev Bras Anestesiol 2001;51:91-7.
43. Saran A, Raipure A, Chauhan RS, Bohra S, Bhargava S. Comparison of intrathecal isobaric ropivacaine with fentanyl and isobaric bupivacaine with fentanyl for spinal anesthesia

for lower abdominal and lower limb surgery. Anaesth Pain Intensive Care 2018;22:38-42.
44. Kumar S, Talwar V, Gupta P, Gogia AR. Comparison of the efficacy of intrathecal isobaric ropivacaine and bupivacaine in day care knee arthroscopy: A randomized controlled trial. Anesth Essays Res 2018;12:859-64.
45. Abhinav K, Desai J. Observational study to compare the effect of intrathecal 0.5% isobaric bupivacaine and 0.75% isobaric ropivacaine for lower abdominal and lower limb surgeries. Indian J Appl Res 2018;8:28-9.
46. Kordcal AR, Kalyanappagol VT, Rao AK, Rao M. Intrathecal ropivacaine versus bupivacaine in endoscopic urological surgeries: A double blind randomized controlled trial. Sri Lankan J Anaesthesiol 2019;27:127-32.
47. Prajwal DS, Kamath SS, Faiaz AF. Comparison of efficacy and safety of intrathecal ropivacaine-fentanyl and bupivacaine-fentanyl in lower abdominal and lower limb surgeries. AmbulSurg 2019;25:114-7.
48. Verma R, Mehrotra S. Comparison between intrathecal isobaric bupivacaine 0.5% with isobaric ropivacaine 0.75% for lower limb orthopaedic surgeries: A double blind randomized controlled study. Int J Contemp Med Res 2017;4:868-71.
49. Adhikari P, Vyas VH, Naseem S, Shelke U. Comparative efficacy and safety of intrathecal ropivacaine versus intrathecal bupivacaine in patients undergoing lower abdominal surgical procedures. Indian J Pain 2020;34:43-6.
50. Kharat PA, Deopujari RC. A comparison of intrathecal 0.5% hyperbaric ropivacaine with 0.5% hyperbaric bupivacaine for elective surgery: A prospective, randomized, double-blind, controlled study. Int J Res Med Sci 2021;9:471-8.
51. Surekha C, Radha MK, Satish Kumar MN, Sharavanan E. A Comparative study of intrathecal isobaric (0.75%) ropivacaine with isobaric (0.5%) bupivacaine for elective lower abdominal/limb surgeries-A Clinical Study. Int J Res Health Sci 2014;2:1172-9.
52. Hazra R. Comparison of the effects of intrathecal bupivacaine, levobupivacaine and ropivacaine in lower abdominal surgery: A double-blind, randomized controlled trial using isobaric preparations. Int J Inf Res Rev 2015;2:636-41.
53. Varun S, Srivastava M, Maurya I, Garg R, Dhama V, Manik YK. A clinical prospective, randomized study to compare intrathecal isobaric bupivacaine–fentanyl and isobaric ropivacaine–fentanyl for lower abdominal and lower limb surgeries. Anaesth Pain Intensive Care 2012;16:237-42.