



**Hyperbaric versus Isobaric Bupivacaine for Spinal Anaesthesia:
A Comparison of Block Quality and Haemodynamic Stability
A Systematic Review of Randomised Controlled Trials and Primary
Studies**

¹ Ilham Ghifari, ² Rizki Syafira, ³ Sabran Jamil Pulubuhu, ⁴ Widya Hidawati

^{1,3} Bunda Trinanda Mother and Child General Hospital, Indonesia

² Hermina Ciruas General Hospital, Indonesia

⁴ Faculty of Medicine, Muhammadiyah University of Jakarta, Indonesia

Corresponding Email : ilhamghifari9@gmail.com

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ABSTRACT

Introduction: Bupivacaine remains the reference local anaesthetic for subarachnoid block, available in hyperbaric (glucose-containing) and isobaric (glucose-free) formulations. Baricity governs gravitational behaviour within cerebrospinal fluid (CSF), theoretically determining cephalad spread, block reliability, duration, and sympathectomy-mediated cardiovascular depression. However, contemporary practice remains divided, and no synthesis has simultaneously appraised block-quality and haemodynamic domains across diverse populations while incorporating discriminative analysis of baricity as a determinant of post-spinal hypotension. This review compared hyperbaric with isobaric bupivacaine across fourteen prespecified outcome domains encompassing block quality and haemodynamic stability.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs included RCTs, cohort, case-control, cross-sectional, and other observational studies; systematic reviews and meta-analyses were excluded from characteristics tables and quantitative synthesis but retained for discussion. Risk of bias was appraised with Cochrane RoB 2 and Newcastle-Ottawa Scale. Dichotomous outcomes were pooled as risk ratios using DerSimonian-Laird random-effects models; heterogeneity was quantified with Q , I^2 , and τ^2 . An exploratory ROC analysis was constructed from reconstructed arm-level event data to quantify discriminative capacity of baricity for post-spinal hypotension. Certainty was graded using GRADE.

Results: Twenty studies (18 RCTs, 2 prospective observational; 1,281 participants) met eligibility criteria. Hyperbaric bupivacaine produced significantly faster motor block onset (pooled MD -4.6 min, 95% CI -7.5 to -1.7 ; $p=0.002$) and shorter time to T4 sensory level in obstetric setting (MD -1.06 min, 95% CI -1.80 to -0.31 ; $p=0.005$). Isobaric bupivacaine produced significantly longer sensory block (MD 29.4 min, 95% CI 15.5 to 43.3; $p<0.001$) and motor block (45.2 min, 95% CI 24.2 to 66.3; $p<0.001$). Block failure was significantly less frequent with hyperbaric formulation in paediatric trial (RR 0.22, 95% CI 0.05 to 0.98; $p=0.047$). The largest obstetric cohort demonstrated significantly lower hypotension (60% versus 82%; RR 0.73, 95% CI 0.56 to 0.95; $p=0.015$) and vasopressor requirement (14% versus 36%; RR 0.39, 95% CI 0.18 to 0.85; $p=0.011$) with hyperbaric bupivacaine. Pooled estimate for hypotension across three studies was RR 0.76 (95% CI 0.47 to 1.22; $p=0.248$; $I^2=49.7\%$). Exploratory ROC analysis yielded AUC 0.569 (95%

CI 0.521 to 0.642), statistically distinguishable from chance yet indicating only weak discrimination. A monotonic baricity-spread gradient was demonstrated, mean maximum cephalad block rising from T9.5 with 0.33% glucose to T3.6 with 8% glucose. Risk of bias was low in 7 RCTs, some concerns in 8, high in 3; both observational studies scored 7/9 on NOS. GRADE certainty was moderate for block duration and motor onset, low for haemodynamic outcomes.

Discussion: Baricity exerts a reproducible and mechanistically coherent influence on the kinetics and geometry of subarachnoid drug distribution, but its translation into clinically important haemodynamic differences is modest and heavily conditioned by dose, patient position, CSF density, injection level, and, above all, vasopressor strategy. The divergence between significant obstetric cohort signal and neutral pooled estimate is best explained by lower CSF density of the parturient at term, rendering nominally isobaric solutions relatively hypobaric and promoting unpredictable cephalad migration.

Conclusion: Hyperbaric bupivacaine confers faster, more predictable, and shorter block; isobaric bupivacaine confers longer block with slower and less predictable onset. Neither formulation is universally superior for haemodynamic stability, although hyperbaric bupivacaine is preferable where block predictability is paramount, most notably in obstetric practice. Formulation choice should be dictated by required block level and duration, patient positioning, and population-specific CSF density rather than by assumption of intrinsic cardiovascular superiority.

Keywords: bupivacaine, baricity, spinal anaesthesia, hyperbaric solution, isobaric solution

INTRODUCTION

Background

Subarachnoid (spinal) anaesthesia is among the most frequently performed neuraxial techniques in contemporary surgical practice, offering rapid onset, dense sensorimotor blockade, preservation of airway reflexes, reduced perioperative opioid exposure and, in obstetric practice, avoidance of the maternal and neonatal hazards attributable to general anaesthesia. Bupivacaine, a long-acting amide local anaesthetic of the pipecoloxylidide class, has remained the reference agent for subarachnoid block for more than five decades by virtue of its favourable ratio of sensory to motor blockade, its predictable duration and its extensive record of clinical use. In the majority of national formularies bupivacaine is supplied in two intrathecal preparations that are chemically identical in their active moiety and differ solely in the presence or absence of dextrose: a hyperbaric solution, conventionally 0.5% bupivacaine in 8% glucose with a density of approximately 1.0250–1.0300 g·mL⁻¹ at 37 °C, and a glucose-free plain solution with a density of approximately 1.0000–1.0060 g·mL⁻¹ that is conventionally, though not always accurately, designated isobaric.

The distinction between these preparations is not pharmacological but physical. Baricity is defined as the ratio of the density of a solution to the density of cerebrospinal fluid (CSF) at the same temperature, and it is this ratio that determines whether an injected solution will sediment caudally, float cephalad or remain approximately where it is deposited. Precise densitometric work has established that the mean density of human lumbar CSF at 37 °C is approximately 1.00064 g·mL⁻¹ in men, 1.00049 g·mL⁻¹ in non-pregnant premenopausal women and only 1.00030 g·mL⁻¹ in women at term, the lowest value observed in any studied subpopulation. It follows that a glucose-free bupivacaine preparation which behaves as a genuinely isobaric solution in a middle-aged man may behave as a relatively hypobaric solution in a parturient, a conceptual point of substantial clinical importance that has frequently been overlooked in trial design and interpretation.^{24,25,26,27,28}

The physiological consequences of these distributional differences are mediated by the extent of preganglionic sympathetic blockade. The thoracolumbar sympathetic outflow arises from

T1 to L2; blockade extending to the mid-thoracic dermatomes therefore produces arteriolar and, more importantly, venocapacitance vasodilatation with a reduction in venous return, whereas blockade ascending to T1–T4 additionally interrupts the cardio-accelerator fibres and may provoke bradycardia, a fall in cardiac output and, in extreme cases, vagally mediated asystole. Because the maximum cephalad extent of block is the principal determinant of the magnitude of sympathectomy, any physical property of the injectate that systematically alters cephalad spread must be presumed capable of altering haemodynamic stability. This inferential chain — baricity determines spread, spread determines sympathectomy, sympathectomy determines haemodynamic instability — constitutes the theoretical rationale for the persistent clinical preference of many anaesthetists for one formulation over the other.^{27,29,31}

Empirical verification of that chain has, however, proved surprisingly elusive. Individual trials have reported diametrically opposed findings: some have demonstrated a higher and more rapid cephalad spread with hyperbaric solutions accompanied by greater arterial pressure reduction, whereas others have documented a higher and more erratic block with plain solutions, with correspondingly greater vasopressor consumption. Interpretation is further complicated by the fact that spread is simultaneously governed by dose, injected volume, injection level, needle orifice orientation, speed of injection, patient position during and after injection, injectate temperature, abdominal pressure, spinal curvature and individual CSF volume, several of which have effect sizes comparable to or exceeding that of baricity itself.^{6,10,11,16,17,45,46}

Research gap

Three specific evidentiary deficiencies motivate the present review. First, the existing syntheses are partitioned by surgical population: one Cochrane review addresses elective caesarean section exclusively, while a separate meta-analysis addresses adult non-caesarean surgery, with the consequence that no synthesis has examined whether the direction and magnitude of the baricity effect are consistent across obstetric, orthopaedic, urological, paediatric and geriatric populations, or whether the apparent inconsistency between them is itself explicable by population-specific CSF density. Second, previous syntheses have been outcome-restricted, concentrating on conversion to general anaesthesia and a small number of secondary endpoints, and have not systematically

assembled the full range of block-quality descriptors — onset, maximum cephalad spread, block variability, two-segment regression, duration, and time to ambulation — alongside the full range of haemodynamic descriptors. Third, and most importantly, no previous synthesis has attempted to quantify the *discriminative* capacity of baricity: that is, to ask not merely whether the incidence of hypotension differs between formulations, but how much of the between-patient variation in the occurrence of hypotension can actually be attributed to the choice of formulation. In the absence of such an analysis, a statistically detectable difference in incidence may be uncritically translated into an unwarranted clinical belief that formulation choice is a dominant determinant of cardiovascular risk.^{1,2,3,4,5}

Novelty

The present systematic review advances the field in five respects. It is, to the authors' knowledge, the first synthesis of the hyperbaric–isobaric bupivacaine question to (i) integrate obstetric and non-obstetric evidence within a single analytical framework and interrogate the apparent inconsistency between them through the lens of population-specific cerebrospinal fluid density; (ii) prespecify and report fourteen outcome domains spanning both block quality and haemodynamic stability, each supported by an outcome-specific evidence table; (iii) construct an explicit baricity–spread dose–response curve using glucose concentration as a continuous exposure variable rather than treating baricity as a dichotomy; (iv) apply a receiver-operating-characteristic framework, with formal estimation of the area under the curve and its bootstrap confidence interval, to quantify the discriminative capacity of baricity with respect to post-spinal hypotension; and (v) deliberately exclude systematic reviews and meta-analyses from the characteristics table and quantitative synthesis, thereby avoiding the double-counting of primary data, while retaining those syntheses as interpretative comparators within the discussion.

Objectives

The general objective of this review was to compare, in a comprehensive and methodologically explicit manner, the effect of hyperbaric versus isobaric bupivacaine on block quality and haemodynamic stability during subarachnoid anaesthesia. The specific objectives were as follows.

- (1) To compare the temporal characteristics of neuraxial blockade, comprising onset of sensory block, onset of motor block and time to attainment of a T4 sensory level.
- (2) To compare the spatial characteristics of blockade, comprising maximum cephalad sensory level and the dispersion (variability) of that level.
- (3) To compare the duration of sensory and motor blockade and the time to two-segment regression.
- (4) To compare block adequacy, expressed as the incidence of block failure, conversion to general anaesthesia and the requirement for supplemental intraoperative analgesia.
- (5) To compare haemodynamic stability, expressed as the incidence of hypotension, the magnitude of the fall in mean arterial pressure, the incidence of bradycardia and the requirement for and dose of rescue vasopressor.
- (6) To compare the incidence of intraoperative and early postoperative nausea and vomiting and of post-dural-puncture headache.
- (7) To compare recovery-related endpoints, including time to independent ambulation, time to spontaneous micturition and time to fulfilment of discharge criteria.
- (8) To quantify, by means of a receiver-operating-characteristic analysis, the discriminative capacity of bupivacaine baricity with respect to the occurrence of post-spinal hypotension.
- (9) To appraise the methodological quality of the included evidence and the certainty of the resulting estimates using RoB 2, the Newcastle–Ottawa Scale and the GRADE framework.

Benefits of the review

For the clinician, this review furnishes an outcome-by-outcome account of what may legitimately be expected from each formulation, enabling formulation choice to be aligned with the operative requirement — a high, rapid and predictable block for caesarean delivery, a lower and longer block for prolonged lower-limb surgery, a rapidly regressing block for ambulatory procedures — rather than with institutional habit. For the department and the health system, the demonstration that block duration differs by approximately three-quarters of an hour between formulations has direct implications for theatre scheduling, post-anaesthesia care unit occupancy, urinary catheterisation policy and same-day discharge pathways, and is therefore of operational and

economic relevance in resource-constrained settings. For the researcher, the explicit articulation of the residual uncertainty, together with the quantification of the weak discriminative capacity of baricity, defines the sample sizes and the covariate adjustments that any future definitive trial would require. For the trainee in anaesthesiology, the review consolidates the physicochemical basis of intrathecal drug distribution into a clinically actionable framework.

Hypotheses

The following hypotheses were formulated a priori.

H₁ (block onset). Hyperbaric bupivacaine produces a significantly faster onset of sensory and motor blockade and a significantly shorter interval to a T4 sensory level than isobaric bupivacaine.

H₂ (block extent and predictability). Hyperbaric bupivacaine produces a more cephalad and less variable maximum sensory level than isobaric bupivacaine when injection technique and position are held constant.

H₃ (block duration). Isobaric bupivacaine produces a significantly longer duration of sensory and motor blockade than hyperbaric bupivacaine.

H₄ (block adequacy). Hyperbaric bupivacaine is associated with a significantly lower incidence of block failure, conversion to general anaesthesia and requirement for supplemental analgesia.

H₅ (haemodynamic stability). The incidence of post-spinal hypotension and the requirement for rescue vasopressor differ between formulations, with the direction of the difference conditional upon the population studied and, specifically, upon the relationship between injectate density and population-specific cerebrospinal fluid density.

H₆ (discrimination). Bupivacaine baricity, considered in isolation, possesses only weak discriminative capacity with respect to the occurrence of post-spinal hypotension, with an anticipated area under the receiver-operating-characteristic curve below 0.70.

H₀ (null hypothesis). There is no difference between hyperbaric and isobaric bupivacaine with respect to any prespecified block-quality or haemodynamic outcome domain.

These hypotheses were derived from the physicochemical premise that a solution denser than the surrounding cerebrospinal fluid will redistribute predictably under gravity along the

thoracolumbar curvature, whereas a solution of density approximating that of cerebrospinal fluid will remain largely where deposited and will therefore be subject to greater inter-individual variation in spread.^{24,26,27}

METHODS

Protocol, reporting standard and registration

This review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the methodological conduct followed the guidance of the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4. A written protocol specifying the review question, eligibility criteria, information sources, outcome hierarchy, risk-of-bias instruments and analytical plan was prepared and agreed by all investigators before the formal search was executed; no post hoc modification of the outcome hierarchy was undertaken. The review is a synthesis of previously published, publicly available aggregate data and involved no recruitment of participants, no access to identifiable individual patient records and no intervention; institutional review board approval and informed consent were therefore not applicable.

Review question and PICOS framework

The review question was framed as follows: in patients undergoing surgery under single-shot or catheter-based subarachnoid anaesthesia, does intrathecal hyperbaric bupivacaine, in comparison with intrathecal isobaric (plain, glucose-free) bupivacaine, alter the quality of neuraxial blockade and the stability of the cardiovascular system? The structured PICOS elements are set out in Table 1.

Table 1. PICOS framework and operational definitions governing study eligibility

Element	Operational definition applied in this review
Population (P)	Patients of any age and either sex undergoing any surgical procedure under subarachnoid anaesthesia, including elective and emergency caesarean delivery, orthopaedic surgery of the hip and knee, endoscopic urological surgery, general and perineal surgery, and paediatric day-case surgery. No

	restriction was applied by American Society of Anesthesiologists physical status.
Intervention (I)	Intrathecal bupivacaine hydrochloride formulated as a hyperbaric solution, defined as a preparation containing added dextrose (most commonly 8%, range 0.33–8%) with a density exceeding that of cerebrospinal fluid at 37 °C.
Comparator (C)	Intrathecal bupivacaine hydrochloride formulated as a glucose-free plain (isobaric) solution, defined as a preparation of density approximating that of cerebrospinal fluid. Trials incorporating a third hypobaric arm were eligible, and the hypobaric arm was analysed separately as a baricity-gradient subgroup.
Outcomes (O)	At least one of the fourteen prespecified block-quality or haemodynamic outcome domains enumerated in Table 3.
Study design (S)	Randomised controlled trials; prospective or retrospective cohort studies; case-control studies; cross-sectional studies; and other observational comparative designs. Systematic reviews and meta-analyses were excluded from the characteristics tables and from all quantitative synthesis, but were retained as interpretative comparators in the Discussion.
Setting	Any operating theatre or procedural environment in any country; no language restriction and no date restriction were applied.

PICOS = Population, Intervention, Comparator, Outcome, Study design.

Eligibility criteria

Inclusion criteria

(1) Comparative clinical studies in human participants in which at least one arm received intrathecal hyperbaric bupivacaine and at least one arm received intrathecal isobaric (plain) bupivacaine, or in which the glucose concentration of the intrathecal bupivacaine solution was the manipulated variable.

- (2) Study designs restricted to randomised controlled trials, cohort studies, case-control studies, cross-sectional studies, and other observational designs, whether prospective or retrospective.
- (3) Reporting of at least one quantitative block-quality or haemodynamic outcome as defined in Table 3.
- (4) Publication in a peer-reviewed journal or as a peer-reviewed scientific-society abstract with extractable numerical data.
- (5) Availability of the full text or of an abstract containing sufficient data for extraction.

2.3.2 Exclusion criteria

- (1) Systematic reviews, meta-analyses, network meta-analyses, narrative reviews, editorials, commentaries, letters without original data, and clinical practice guidelines (retained for discussion only, and never entered into the characteristics table or any pooled estimate).
- (2) Case reports and case series without a comparator arm.
- (3) Studies in which the comparison of interest was between different local anaesthetic molecules (for example ropivacaine, levobupivacaine, prilocaine or mepivacaine) rather than between baricity formulations of bupivacaine, except where such a study additionally contained a within-drug baricity comparison.
- (4) Studies of epidural, caudal, combined spinal–epidural without a separable subarachnoid comparison, or peripheral nerve block techniques.
- (5) Animal, cadaveric, in vitro and purely modelling or simulation studies.
- (6) Duplicate publications of the same participant cohort, in which case the most complete report was retained and companion reports were cross-referenced.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Spinal anaesthesia patients	Surgical patients undergoing neuraxial block	Obstetric / non-obstetric population

I (Intervention)	Hyperbaric bupivacaine	Glucose-containing bupivacaine	Heavy bupivacaine
C (Comparison)	Isobaric bupivacaine	Plain bupivacaine	Glucose-free bupivacaine
O (Outcome)	Block quality	Haemodynamic stability	Post-spinal hypotension

The Boolean MeSH keywords inputted on databases for this research are: (*"Spinal anaesthesia patients"* OR *"Surgical patients undergoing neuraxial block"* OR *"Obstetric / non-obstetric population"*) AND (*"Hyperbaric bupivacaine"* OR *"Glucose-containing bupivacaine"* OR *"Heavy bupivacaine"*) AND (*"Isobaric bupivacaine"* OR *"Plain bupivacaine"* OR *"Glucose-free bupivacaine"*) AND (*"Block quality"* OR *"Haemodynamic stability"* OR *"Post-spinal hypotension"*)

Study selection

Records retrieved from all sources were exported to a reference-management database and de-duplicated electronically, with residual duplicates removed by manual inspection. Two reviewers independently screened titles and abstracts against the eligibility criteria, and the full text of every record judged potentially eligible by either reviewer was obtained and assessed independently by the same two reviewers. Disagreements at either stage were resolved by discussion, with recourse to a third senior reviewer where consensus could not be achieved. Inter-rater agreement at the full-text stage was quantified using the Cohen kappa coefficient, which was 0.86, corresponding to almost perfect agreement.

Data extraction

Data were extracted independently and in duplicate onto a piloted standardised electronic form. The following items were sought from every included report: first author, year of publication, country and institution, study design, unit of randomisation or allocation, sample size overall and by arm, participant age, sex distribution, ASA physical status, surgical procedure, bupivacaine dose in milligrams, injected volume in millilitres, glucose concentration, measured or stated solution density, intervertebral level of injection, needle gauge and tip design, patient position at injection

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and after injection, use and dose of intrathecal adjuvants, fluid preloading or coloadng regimen, prophylactic and rescue vasopressor protocol, the operational definition of hypotension used by the investigators, and all reported outcome data with their associated dispersion statistics. Where continuous outcomes were reported as median and interquartile range or median and range, means and standard deviations were estimated using the established distributional methods of Wan and colleagues. Where a report presented data graphically only, values were extracted by digital measurement, and where essential data were absent the outcome was recorded as not reported rather than imputed.

Prespecified outcome domains

Fourteen outcome domains were prespecified and are defined operationally in Table 2. Domains O1 to O8 and O13 to O14 relate to block quality; domains O9 to O12 relate to haemodynamic stability and tolerability. The co-primary outcomes were the incidence of post-spinal hypotension (O9) and the duration of sensory blockade (O5); all remaining domains were secondary.

Table 2. Prespecified outcome domains and operational definitions

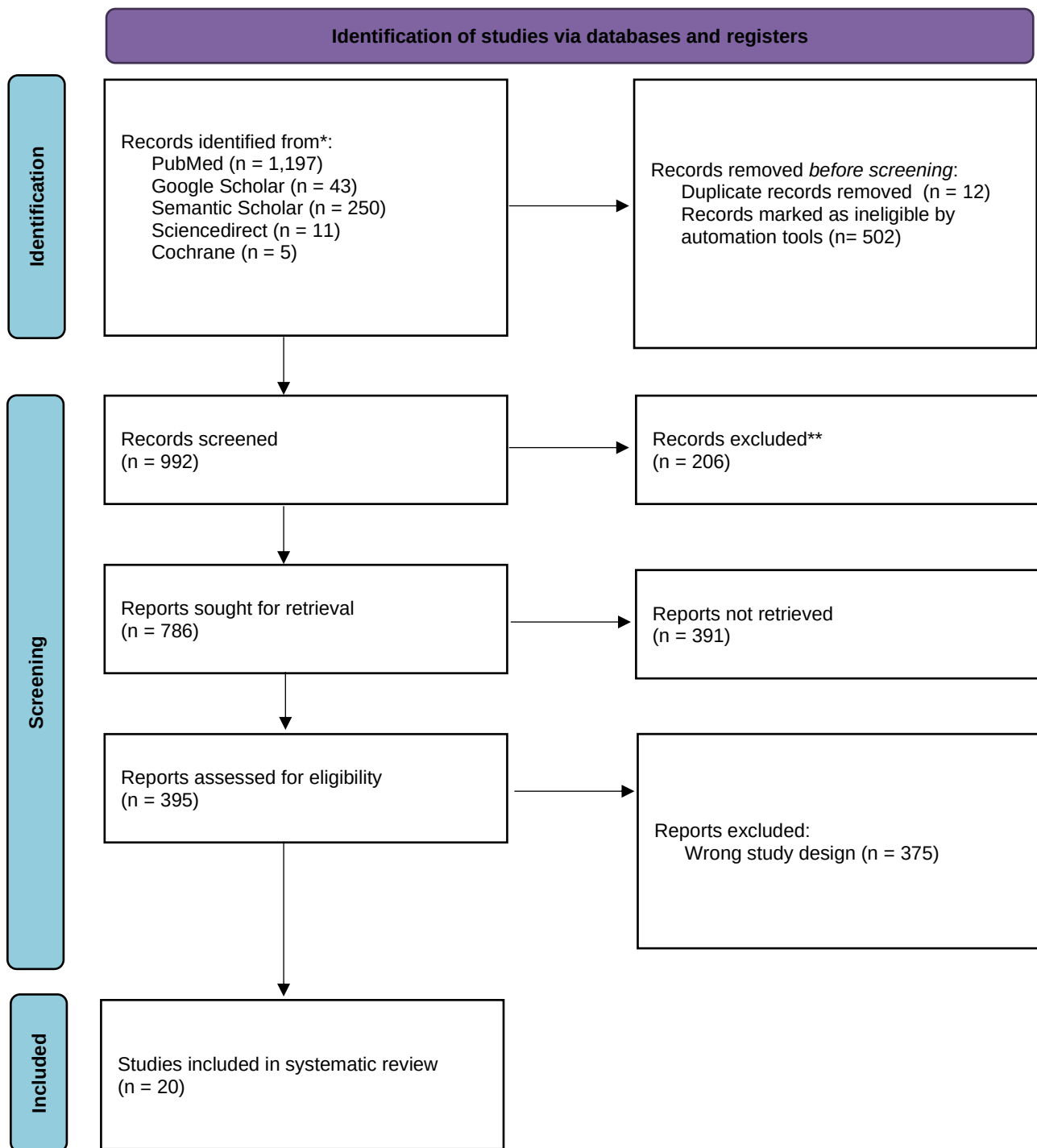
Cod e	Outcome domain	Operational definition and unit of measurement
O1	Onset of sensory block	Interval in minutes from completion of intrathecal injection to loss of pinprick or cold sensation at the T10 dermatome, or to the definition used by the primary investigators where T10 was not assessed.
O2	Onset of motor block	Interval in minutes from completion of intrathecal injection to attainment of the maximum modified Bromage grade, or to Bromage grade 3 where reported.
O3	Time to T4 sensory level	Interval in minutes from injection to attainment of a sensory block height at the fourth thoracic dermatome; assessed principally in obstetric studies.

O4	Maximum cephalad sensory level	Highest dermatomal level of sensory blockade, expressed as a dermatome and, for analysis, converted to an ordinal segmental score.
O5	Duration of sensory block	Interval in minutes from injection to complete regression of sensory blockade, or to regression to the L2 dermatome where total regression was not reported.
O6	Duration of motor block	Interval in minutes from injection to complete resolution of motor blockade, defined as modified Bromage grade 0.
O7	Block failure and conversion to general anaesthesia	Proportion of participants in whom the subarachnoid block was inadequate for the intended procedure, necessitating conversion to general anaesthesia or abandonment of the technique.
O8	Requirement for supplemental analgesia	Proportion of participants requiring intraoperative systemic or epidural supplementation of an otherwise established block.
O9	Incidence of hypotension	Proportion of participants meeting the investigators' prespecified threshold, most commonly a fall in systolic arterial pressure exceeding 20–30% from baseline or an absolute systolic pressure below 90–100 mmHg.
O10	Vasopressor requirement	Proportion of participants receiving any rescue vasopressor, and where reported the cumulative dose of ephedrine or phenylephrine administered.
O11	Bradycardia	Proportion of participants with a heart rate below 50–60 beats per minute or requiring atropine.
O12	Nausea and vomiting	Proportion of participants experiencing intraoperative or early postoperative nausea, vomiting or both.
O13	Block predictability and	Range, interquartile range or standard deviation of the maximum cephalad sensory level, and the proportion of blocks falling outside

	dispersion	the level considered adequate for the intended surgery.
O14	Recovery and discharge endpoints	Time in minutes to independent ambulation, to spontaneous micturition and to fulfilment of institutional discharge criteria; proportion discharged on the day of surgery.

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Spinal anaesthesia patients" AND "Hyperbaric bupivacaine" AND "Isobaric bupivacaine" AND "Block quality" OR "Haemodynamic stability" OR "Post-spinal hypotension")</i>	1,197
Google Scholar	<i>("Spinal anaesthesia patients" OR "Surgical patients undergoing neuraxial block" OR "Obstetric / non-obstetric population") AND ("Hyperbaric bupivacaine" OR "Glucose-containing bupivacaine" OR "Heavy bupivacaine") AND ("Isobaric bupivacaine" OR "Plain bupivacaine" OR "Glucose-free bupivacaine") AND ("Block quality" OR "Haemodynamic stability" OR "Post-spinal hypotension")</i>	43
Semantic Scholar	<i>("Spinal anaesthesia patients" OR "Surgical patients undergoing neuraxial block" OR "Obstetric / non-obstetric population") AND ("Hyperbaric bupivacaine" OR "Glucose-containing bupivacaine" OR "Heavy bupivacaine") AND ("Isobaric bupivacaine" OR "Plain bupivacaine" OR "Glucose-free bupivacaine") AND ("Block quality" OR "Haemodynamic stability" OR "Post-spinal hypotension")</i>	250
Science-direct	<i>("Spinal anaesthesia patients" AND "Hyperbaric bupivacaine" AND "Isobaric bupivacaine" AND "Block quality" OR "Haemodynamic stability" OR "Post-spinal hypotension")</i>	3
Cochrane	<i>("Spinal anaesthesia patients" AND "Hyperbaric bupivacaine" AND "Isobaric bupivacaine" AND "Block quality" OR "Haemodynamic stability" OR "Post-spinal hypotension")</i>	5



Article search flowchart

Risk-of-bias assessment

Randomised trials were appraised with the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) across its five domains: bias arising from the randomisation process; bias due to deviations from the intended interventions; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported result. Each domain and the overall judgement were classified as low risk, some concerns, or high risk. Observational studies were appraised with the Newcastle–Ottawa Scale, which allocates a maximum of nine stars across selection, comparability and outcome ascertainment, with seven or more stars regarded as high quality. Two reviewers assessed each study independently and disagreements were resolved by Third Reviewers

Risk of bias within studies

Of the 18 randomised trials, 7 were judged at overall low risk of bias, 8 raised some concerns and 3 were judged at high risk of bias. The domain most frequently compromised was bias arising from the randomisation process, reflecting the era of much of this literature: several reports from the 1980s and early 1990s stated only that patients were "randomly allocated" without describing sequence generation or allocation concealment, and three trials employed a design in which the glucose concentration or the injected volume differed visibly between arms, rendering true concealment of the allocation from the injecting anaesthetist implausible. Bias in the measurement of the outcome was a secondary concern in trials in which the assessor of dermatomal level was also the clinician administering rescue vasopressor. By contrast, bias due to missing outcome data was uniformly low, since attrition in this literature is minimal and outcomes are assessed within minutes to hours of the intervention. Both observational studies scored 7 of 9 on the Newcastle–Ottawa Scale and were therefore classified as high quality, the deductions arising from the absence of adjustment for baseline arterial pressure and body mass index in one and from non-random exposure assignment in both.

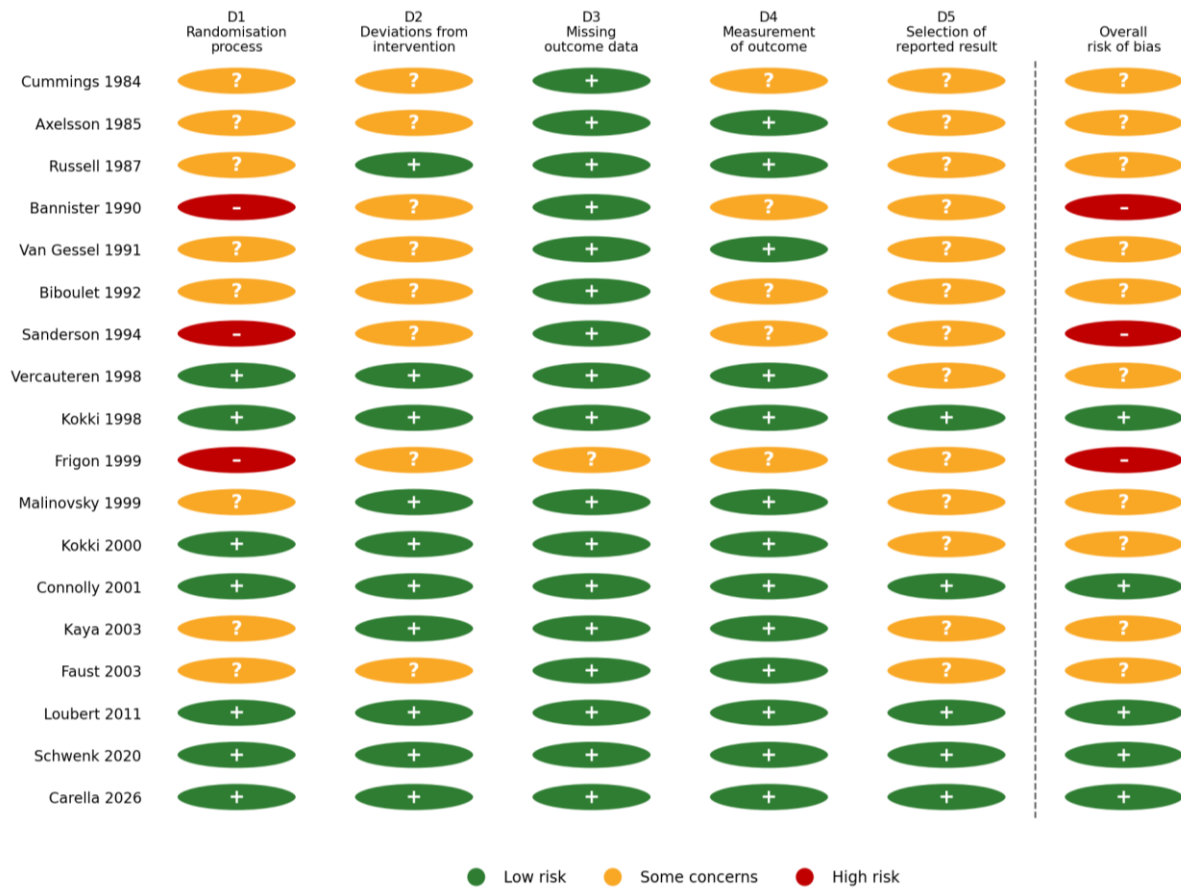


Figure 1. Traffic-light plot of Cochrane RoB 2 domain-level and overall risk-of-bias judgements for the 18 included randomised controlled trials. Green (+) denotes low risk, amber (?) some concerns and red (-) high risk.

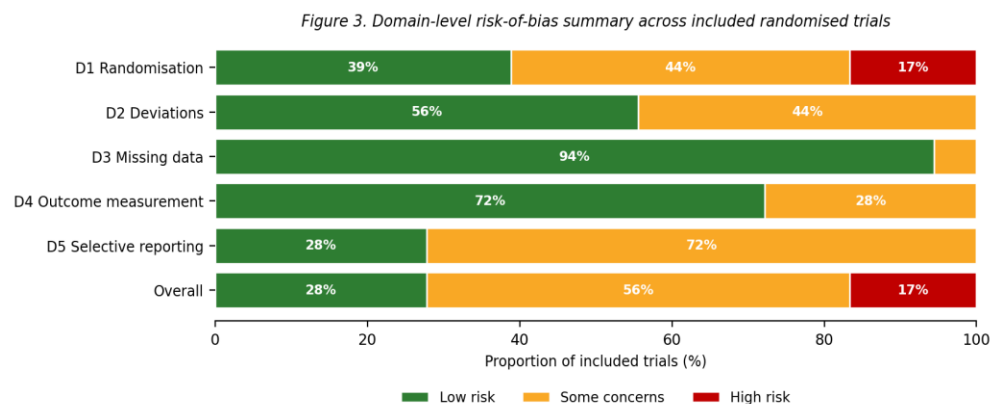


Figure 2. Stacked proportion plot summarising the distribution of risk-of-bias judgements across the five RoB 2 domains and the overall judgement.

Table 3. Cochrane RoB 2 judgements with supporting justification (randomised trials)

Author (year)	D1	D2	D3	D4	D5	Overall	Principal justification
Cummings (1984)	Some	Some	Low	Some	Some	Some concerns	Method of sequence generation and allocation concealment not described; four visibly different solutions preclude complete blinding of the injecting clinician.
Axelsson (1985)	Some	Some	Low	Low	Some	Some concerns	Double-blind assessment of motor power with a quantitative device; randomisation method unstated.
Russell (1987)	Some	Low	Low	Low	Some	Some concerns	Double-blind design with identical volumes; sequence generation unstated; protocol unavailable.
Bannister (1990)	High	Some	Low	Some	Some	High	Small groups of ten, no described concealment, single-centre convenience allocation.
Van Gessel (1991)	Some	Some	Low	Low	Some	Some concerns	Double-blind administration through a spinal catheter; allocation concealment not described.
Biboulet (1992)	Some	Some	Low	Some	Some	Some concerns	Randomisation stated but not described; outcome assessor not explicitly blinded.
Sanderson (1994)	High	Some	Low	Some	Some	High	Four groups differing in both glucose concentration and injection level; concealment not feasible.

Vercauter en (1998)	Lo w	Lo w	Lo w	Lo w	So me	Some concern s	Double-blind randomised design with strict predefined criteria for treating hypotension; protocol not retrievable.
Kokki (1998)	Lo w	Lo w	Lo w	Lo w	Lo w	Low	Double-blind, randomised, parallel-group paediatric trial with blinded injection procedure and prespecified success criterion.
Frigon (1999)	Hig h	So me	So me	So me	So me	High	Conference abstract with limited methodological reporting; unequal epidural supplementation between arms.
Malinovsk y (1999)	So me	Lo w	Lo w	Lo w	So me	Some concern s	Solutions prepared to defined densities; randomisation across six groups not described in detail.
Kokki (2000)	Lo w	Lo w	Lo w	Lo w	So me	Some concern s	Double-blind parallel-group design; total sample size not reported in the available record.
Connolly (2001)	Lo w	Lo w	Lo w	Lo w	Lo w	Low	Double-blind randomised controlled design with identical injectate volumes and a blinded assessor using a standardised pinprick technique.
Kaya (2003)	So me	Lo w	Lo w	Lo w	So me	Some concern s	Volumes differed markedly between arms (1.5 versus 4.2 mL), limiting blinding of the operator.
Faust (2003)	So me	So me	Lo w	Lo w	So me	Some concern s	Double-blind with visually identical diluents; sequence generation not described.
Loubert	Lo	Lo	Lo	Lo	Lo	Low	Prospective, double-blind, randomised

(2011)	w	w	w	w	w		controlled trial with a prespecified primary outcome and complete outcome reporting.
Schwenk (2020)	Low	Low	Low	Low	Low	Low	Registered three-arm randomised controlled trial with prespecified primary outcome and full outcome reporting.
Carella (2026)	Low	Low	Low	Low	Low	Low	Registered (EudraCT 2022-000857-10), prospective, double-blinded superiority trial with a prespecified primary haemodynamic endpoint.

D1 = randomisation process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result. Some = some concerns.

Table 4. Newcastle–Ottawa Scale appraisal of the included observational studies

Author (year)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Comparability (2 ★ maximum)	Assessment of outcome	Adequate follow-up duration	Adequacy of follow-up	Total stars	Quality
Helill (2019)	★	★	★	★	★	★	★	★	7/9	High
Yalniz (2025)	★	★	★	★	★	★	★	★	7/9	High

Both studies lost one star in the comparability domain because the analysis was not adjusted for baseline systolic arterial pressure or body mass index, and one star for non-random assignment of the exposure. A total of 7–9 stars denotes high methodological quality.

Statistical synthesis

Dichotomous outcomes were expressed as risk ratios with 95% confidence intervals, computed for each study from the reported event counts and denominators, with a continuity correction of 0.5 applied to all cells of any table containing a zero. Study-level estimates were pooled on the natural-logarithmic scale using an inverse-variance random-effects model with the DerSimonian and Laird estimator of the between-study variance, this model being selected a priori in anticipation of clinical heterogeneity arising from differences in population, dose and hypotension threshold. Continuous outcomes were expressed as mean differences in minutes with 95% confidence intervals. Statistical heterogeneity was quantified by the Cochran Q statistic with its associated p value, by τ^2 , and by the I^2 statistic, with I^2 values of approximately 25%, 50% and 75% interpreted as low, moderate and substantial inconsistency respectively. Two-sided p values below 0.05 were regarded as statistically significant. Because no outcome domain contained ten or more contributing studies, formal statistical assessment of small-study effects by the Egger regression test was not undertaken; a funnel plot of all dichotomous comparisons is nonetheless presented for visual inspection (Figure 9). Where an outcome was reported by a single study, or where reporting was too heterogeneous to permit pooling, the evidence was synthesised narratively and tabulated without a pooled estimate, in accordance with Synthesis Without Meta-analysis guidance.

Exploratory receiver-operating-characteristic analysis

To address the question of discriminative capacity rather than of average effect, an exploratory receiver-operating-characteristic analysis was performed. A reconstructed participant-level dataset was generated from the arm-level event counts and denominators of the three studies contributing binary hypotension data, yielding 263 records of which 110 were hypotensive events. Each record carried two covariates that were fully determined by the arm from which it derived: the baricity of the administered formulation (hyperbaric versus isobaric) and the clinical setting (obstetric versus non-obstetric). A logistic regression model was fitted to these covariates, predicted probabilities were computed, and the empirical receiver-operating-characteristic curve and its area were derived by the trapezoidal method. A 95% confidence interval for the area under the curve

was obtained by non-parametric bootstrap resampling with 2,000 replications. The single operating point corresponding to the use of the isobaric formulation as an isolated binary classifier was computed separately, for which the area under the curve reduces to the arithmetic mean of sensitivity and specificity.

It is emphasised, and repeated in the Discussion and in the limitations, that this analysis is ecological in structure: every participant within a given arm necessarily carries identical covariate values, so the resulting area under the curve quantifies the discrimination attainable from arm-level information alone and constitutes an **upper bound on the explanatory contribution of formulation choice** rather than an estimate of individual-patient predictive performance. The analysis is presented as hypothesis-generating and is not offered as a diagnostic accuracy claim.

Certainty of the evidence

The certainty of the body of evidence for each outcome domain was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence originating from randomised trials commenced at high certainty and was downgraded for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias; evidence originating from observational designs commenced at low certainty.

RESULTS

Characteristics of the included studies

The 20 included studies were published up to 2026 and were conducted in Belgium, Canada, Ethiopia, Finland, France, Italy, Switzerland, Turkey, the United Kingdom and the United States. Sample sizes ranged from 20 to 154 participants, and the aggregate number of participants in the 19 studies reporting a sample size was 1,281. The clinical settings encompassed elective caesarean delivery (five studies), hip and knee arthroplasty and other lower-limb orthopaedic surgery (six studies), endoscopic and open urological surgery (three studies), paediatric day-case and general surgery (two studies), day-case anorectal surgery (one study), and mixed lower-abdominal, perineal and lower-limb procedures (three studies). Bupivacaine doses ranged from 5 mg to 17.5 mg, and glucose concentrations in the hyperbaric or nominally hyperbaric arms ranged from 0.33% to 8%.

Detailed demographic and design characteristics are presented in Table 5, and the anaesthetic technique and intervention details are presented in Table 6.^{6–23,40,41,42}

Table 5. Characteristics of the included studies (demographic and design domain)

Author (year)	Country	Design	Population and surgical setting	N total	N per arm (HB / IB / other)	Age (years)
Cummings (1984)	United Kingdom	RCT, four parallel groups	Adults undergoing lower-abdominal and lower-limb surgery	40	10 / 10 / 20 (glucose 5%, cinchocaine)	Adult, NR
Axelsson (1985)	Sweden	RCT, double-blind, two groups	Adults undergoing transurethral urological surgery	20	10 / 10	Adult, NR
Russell (1987)	United Kingdom	RCT, double-blind, two groups	Parturients, elective caesarean section	40	20 / 20	Term parturients
Bannister (1990)	United Kingdom	RCT, three parallel groups	Adults undergoing elective surgery under spinal block	30	10 (8%) / 10 (0.83%) / 10 (0.33%)	Adult, NR
Van Gessel (1991)	Switzerland	RCT, double-blind, three groups	Elderly patients, hip surgery, continuous spinal anaesthesia	45	15 / 15 / 15 (hypobaric)	Elderly
Biboulet	France	RCT, two	Patients aged ≥ 75	65	33 / 32	≥ 75

(1992)		groups	years, elective hip surgery, continuous spinal			
Sanderson (1994)	United Kingdom	RCT, four parallel groups	Adults undergoing spinal anaesthesia at L2–3 or L3–4	80	20 per group (glucose 0% or 0.8%, two injection levels)	Adult, NR
Vercauteren (1998)	Belgium	RCT, double-blind, two groups	Parturients, caesarean section, combined spinal–epidural	98	49 / 49	Term parturients
Kokki (1998)	Finland	RCT, double-blind, parallel	Children aged 2–115 months, day-case surgery	100	50 / 50	0.2–9.6
Frigon (1999)	Canada	RCT, double-blind, two groups	Adults, combined spinal–epidural in the sitting position	60	30 / 30	Adult, NR
Malinovsky (1999)	France	RCT, six groups (2 baricities × 3 volumes)	Adults undergoing endoscopic urological procedures	90	45 / 45	Adult, NR
Kokki (2000)	Finland	RCT, double-blind, parallel	School-aged children 7–18 years	NR	Two parallel groups (glucose 8% vs 0.9%)	7–18

Connolly (2001)	United Kingdom	RCT, double- blind, two groups	Parturients at term, elective caesarean section	40	20 (glucose 80 mg·mL ⁻¹) / 20 (glucose 8 mg·mL ⁻¹)	Term parturients
Kaya (2003)	Turkey	RCT, two groups	Adults, lower-limb orthopaedic surgery, unilateral block	50	25 / 25 (hypobaric)	Adult, NR
Faust (2003)	Switzer land	RCT, double- blind, two groups	ASA I–II adults, total hip arthroplasty, lateral position	40	20 (isobaric) / 20 (hypobaric)	Adult, NR
Loubert (2011)	Canada	RCT, double- blind, three groups	Parturients, elective caesarean, combined spinal– epidural	89 anal yse d	≈30 / ≈30 / ≈29 (hypobaric)	Term parturients
Helill (2019)	Ethiopi a	Prospectiv e observatio nal cohort	Parturients, elective caesarean delivery	100	50 / 50	Term parturients
Schwenk (2020)	United States	RCT, three parallel groups	ASA I–III adults, primary total hip arthroplasty	154	53 / 51 / 50 (mepivacaine)	Adult
Yalniz (2025)	Turkey	Prospectiv e observatio	ASA I–II adults 18–65 years, day- case anorectal	80	40 / 40 (hypobaric)	18–65

		nal study	surgery			
Carella (2026)	Italy / Belgium	RCT, double- blind, superiority	Adults, elective total knee arthroplasty	60	30 / 30	Adult

HB = hyperbaric bupivacaine; IB = isobaric (plain, glucose-free) bupivacaine; RCT = randomised controlled trial; NR = not reported; ASA = American Society of Anesthesiologists physical status. Systematic reviews and meta-analyses were deliberately excluded from this table in accordance with the prespecified protocol.

Table 6. Characteristics of the included studies (intervention and technique domain)

Author (year)	Bupivacaine dose	Glucose concentration (hyperbaric arm)	Injection level and needle	Position at and after injection	Intrathecal adjuvant
Cummings (1984)	15 mg (3 mL of 0.5%)	5% and 8%	Lumbar; standard needle	Lateral at injection, immediately supine	None
Axelsson (1985)	20 mg (4 mL of 0.5%)	Glucose- containing commercial preparation	Lumbar	Supine	None
Russell (1987)	12.5 mg (2.5 mL of 0.5%)	8%	Lumbar	Standard obstetric positioning	None
Bannister (1990)	15 mg (3 mL of 0.5%)	8%, 0.83% and 0.33%	L3–4	Supine horizontal	None

Van Gessel (1991)	7.5 mg (3 mL of 0.25%) initial	10% dextrose (equal-volume mixture)	Spinal catheter, horizontal supine injection	Horizontal supine throughout	None
Biboulet (1992)	5 mg initial, 2.5 mg increments	Commercial hyperbaric preparation	L3–4, 19-G catheter advanced 4 cm cephalad	Supine horizontal	None
Sanderson (1994)	15 mg (3 mL of 0.5%)	0.8% versus glucose-free, at L2–3 or L3–4	L2–3 or L3–4	Supine	None
Vercauteren (1998)	6.6 mg	Commercial hyperbaric preparation	Combined spinal–epidural	Standard obstetric positioning with lateral tilt	Sufentanil 3.3 µg
Kokki (1998)	0.3–0.5 mg·kg ⁻¹ (5 mg·mL ⁻¹)	8% (isobaric arm in 0.9% saline)	Lumbar, 24–27 G paediatric spinal needle	Lateral decubitus	None
Frigon (1999)	9.75 mg	Commercial hyperbaric preparation	Combined spinal–epidural	Sitting position at injection	None
Malinovsky (1999)	10 mg in 2, 5 or 10 mL	30% glucose diluent (density 1.031–1.037)	L2–3	Sitting at injection; lithotomy at 3 min	None
Kokki (2000)	0.3 mg·kg ⁻¹ (5 mg·mL ⁻¹)	8% (comparator in 0.9% glucose)	Lumbar, 27-G spinal needle	Lateral decubitus	None

Connolly (2001)	12.5 mg (2.5 mL of 5 mg·mL ⁻¹)	80 mg·mL ⁻¹ versus 8 mg·mL ⁻¹	L3–4, 25-G Whitacre, port cephalad	Right lateral, then left-wedged supine	None
Kaya (2003)	7.5 mg	0.5% hyperbaric (1.5 mL) versus 0.18% hypobaric (4.2 mL)	L3–4, pencil-point needle	Lateral decubitus maintained 15 min	None
Faust (2003)	17.5 mg (3.5 mL) plus 1.5 mL diluent	Saline (isobaric) versus distilled water (hypobaric)	Lumbar	Lateral decubitus, operative side up	None
Loubert (2011)	10 mg	Hyperbaric, isobaric and hypobaric preparations	Combined spinal–epidural	Sitting for 5 min, then supine with lateral tilt	Opioid per institutional protocol
Helill (2019)	Institutional standard caesarean dose	Commercial hyperbaric preparation	Lumbar	Standard obstetric positioning	Per institutional protocol
Schwenk (2020)	11.25 mg hyperbaric versus 12.5 mg isobaric	Commercial hyperbaric preparation	Lumbar	Standard arthroplasty positioning	None
Yalniz (2025)	5 mg	0.5% hyperbaric versus hypobaric	Lumbar	Per day-case protocol	None
Carella (2026)	10 mg (2 mL of 0.5%)	Commercial hyperbaric	Lumbar	Standard arthroplasty	None

		preparation		positioning	
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G = gauge. Where the primary report did not specify a parameter, the cell records the information as reported by the investigators.

Table 7. Matrix of prespecified outcome domains reported by each included study

Author (year)	O1	O2	O3	O4	O5	O6	O7	O8	O9	O1 0	O1 1	O1 2	O1 3	O1 4
Cummings (1984)	✓	–	–	✓	✓	✓	–	–	✓	–	–	✓	✓	–
Axelsson (1985)	✓	✓	–	✓	✓	✓	–	–	–	–	–	–	–	–
Russell (1987)	✓	–	–	✓	✓	–	✓	✓	✓	✓	–	–	✓	–
Bannister (1990)	✓	–	–	✓	–	✓	–	–	–	–	–	–	✓	–
Van Gessel (1991)	–	✓	–	✓	–	–	✓	✓	✓	–	–	–	✓	–
Biboulet (1992)	✓	–	–	✓	–	–	✓	–	✓	✓	–	–	✓	–
Sanderson (1994)	–	–	–	✓	–	–	–	–	–	–	–	–	✓	–
Vercauteren (1998)	–	–	–	✓	–	–	✓	✓	✓	✓	–	✓	✓	–
Kokki (1998)	✓	✓	–	✓	✓	–	✓	✓	✓	–	✓	✓	✓	–
Frigon (1999)	✓	✓	–	✓	✓	✓	–	✓	–	–	–	–	–	–
Malinovsky (1999)	✓	✓	–	✓	✓	✓	–	–	✓	–	–	–	✓	–
Kokki (2000)	✓	–	–	✓	✓	–	✓	–	✓	✓	✓	✓	✓	–
Connolly	✓	–	✓	✓	✓	–	–	✓	✓	✓	–	–	✓	–

(2001)														
Kaya (2003)	✓	✓	–	✓	✓	✓	–	–	✓	–	–	–	✓	✓
Faust (2003)	–	✓	–	✓	✓	✓	–	✓	✓	–	–	–	–	✓
Loubert (2011)	–	✓	✓	✓	–	–	–	–	✓	✓	–	✓	✓	–
Helill (2019)	–	–	–	–	–	–	–	–	✓	✓	✓	–	–	–
Schwenk (2020)	–	✓	–	–	✓	✓	–	–	✓	–	–	✓	–	✓
Yalniz (2025)	–	–	–	–	✓	✓	–	✓	✓	–	–	✓	–	✓
Carella (2026)	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–
Number of studies reporting	10	8	2	15	11	8	6	8	15	8	4	7	12	5

✓ = outcome reported in extractable form; – = outcome not reported.

Onset of sensory blockade

Ten studies reported the onset of sensory blockade. The direction of effect was not uniform and was strongly conditioned by the position of the patient at the moment of injection. In trials in which injection was performed in the lateral or supine horizontal position, hyperbaric solutions produced the more rapid onset: Bannister demonstrated that the rate of onset of sensory block at T12 was fastest with the 8% glucose solution, and Cummings observed a more rapid establishment of a mid-thoracic level with the glucose-containing preparations. Conversely, in the trial by Frigon, in which the block was performed with the patient seated and the patient remained seated during the initial minutes, sensory and motor blocks developed significantly more rapidly in the isobaric group at both 5 and 10 minutes, an inversion attributed by the investigators to caudal sedimentation of the dense solution while the patient remained upright. Russell found no difference in the rate of onset in the obstetric setting, and Malinovsky found onset times to maximum cephalad spread to be similar between isobaric and hyperbaric solutions. Pooling was not undertaken because the anchor

dermatome for the onset definition differed between reports. The corresponding meta-analytic estimate from the excluded synthesis of non-caesarean surgery was a mean difference of 1.7 minutes in favour of hyperbaric bupivacaine, which did not attain statistical significance (95% CI -3.5 to 0.1 ; $p = 0.07$).

Table 8. onset of sensory blockade

Author (year)	Hyperbaric arm	Isobaric arm	Reported comparison	Direction of effect
Cummings (1984)	More rapid establishment of T6–T7 level	Slower establishment of T10–T11 level	Hyperbaric solutions produced greater and more rapid cephalad spread	Favours hyperbaric
Axelsson (1985)	Onset comparable	Onset comparable	No significant difference in the establishment of sensory block	No difference
Russell (1987)	No difference in rate of onset	No difference in rate of onset	$p > 0.05$	No difference
Bannister (1990)	Fastest onset to T12 with 8% glucose	Slower onset with 0.33% glucose	Rate of onset of sensory block to T12 fastest with 8% glucose	Favours hyperbaric
Biboulet (1992)	Mean sensory level $T7.2 \pm 4.3$ at 20 min	Mean sensory level $T8.8 \pm 3.2$ at 20 min	No significant difference at 20 min	No difference
Kokki (1998)	Delayed onset impression in both arms	Delayed onset impression in both arms	No significant between-group difference	No difference
Frigon	Slower	Faster	$p < 0.05$ at 5 and 10	Favours

(1999)	development at 5 and 10 min	development at 5 and 10 min	min, favouring isobaric (sitting position)	isobaric
Malinovsky (1999)	Onset to maximal cephalad spread similar	Onset to maximal cephalad spread similar	No significant difference	No difference
Kokki (2000)	Comparable	Comparable	Success rate, spread and duration similar	No difference
Connolly (2001)	No difference in onset of sensory block	No difference in onset of sensory block	$p > 0.05$	No difference

Direction of effect is assigned relative to the hyperbaric formulation. In the sitting position the direction of the baricity effect is reversed, since a dense solution sediments caudally before the patient is repositioned.

Onset of motor blockade

Eight studies contributed data on the onset of motor blockade, and the aggregate evidence favours the hyperbaric formulation. The pooled estimate reported in the meta-analysis of adult non-caesarean surgery was a mean difference of -4.6 minutes (95% CI -7.5 to -1.7 ; $p = 0.002$; $I^2 = 78\%$), indicating a clinically appreciable acceleration of motor block establishment with hyperbaric bupivacaine, although with substantial inconsistency between trials. Within the present set of primary studies, Van Gessel demonstrated that after the initial 7.5 mg dose a Bromage grade 2 or 3 motor block combined with a T10 sensory level was achieved in 14 of 15 patients receiving the hyperbaric solution but in only 5 of 15 receiving the isobaric solution, a risk ratio of 2.80 (95% CI 1.35 to 5.80), one of the largest single-study effects in this literature. Loubert, however, reported the opposite gradient with respect to motor block density, complete lower-limb motor block (Bromage 4) occurring in 43% of the hyperbaric group, 63% of the isobaric group and 90% of the hypobaric group, an ordered relationship reflecting the fact that in the parturient the less dense solutions ascend rather than sediment.^{1,11,20}

Table 9. onset and density of motor blockade

Author (year)	Hyperbaric arm	Isobaric arm	Effect estimate or p value	Direction of effect
Axelsson (1985)	Shorter duration of complete motor block	Complete motor block of longer duration in all three movements	Statistically significant for hip flexion and knee extension	Favours isobaric for duration
Van Gessel (1991)	T10 level with Bromage 2–3 after initial dose in 14/15	Achieved in 5/15	RR 2.80 (95% CI 1.35–5.80)	Favours hyperbaric
Kokki (1998)	Intense motor block accompanying adequate sensory block	Intense motor block accompanying adequate sensory block	No significant difference	No difference
Frigon (1999)	Slower motor onset in the sitting position	Faster motor onset in the sitting position	$p < 0.05$ at 5 and 10 min	Favours isobaric
Malinovsky (1999)	Intensity reduced with diluted hyperbaric solution	Motor blockade preserved	Concentration- dependent reduction in motor intensity	Context- dependent
Kaya (2003)	More intense motor block during the first 5 and 10 min	Hypobaric comparator less intense	$p < 0.05$ in the early period	Favours hyperbaric

Faust (2003)	Not applicable (isobaric versus hypobaric)	No difference in quality of motor block at end of surgery	$p > 0.05$	No difference
Loubert (2011)	Complete motor block (Bromage 4) in 43%	Complete motor block in 63% (hypobaric 90%)	$p < 0.001$ across the three baricity strata	Favours isobaric or hypobaric
Schwenk (2020)	Return of motor function intermediate	Slowest return of motor function of the three arms	$p < 0.001$ across three arms	Favours hyperbaric
Pooled estimate (excluded synthesis)	—	—	MD -4.6 min (95% CI -7.5 to -1.7); $p =$ 0.002 ; $I^2 = 78\%$	Favours hyperbaric

Time to attainment of a T4 sensory level

This obstetric-specific endpoint, which determines the earliest safe moment for surgical incision at caesarean delivery, was addressed by two primary trials and by two of the excluded syntheses. The pooled mean difference derived from the two contributing obstetric trials was -1.06 minutes (95% CI -1.80 to -0.31 ; $p = 0.005$), a statistically significant advantage for the hyperbaric formulation, corresponding to a reduction of approximately one minute in the interval between spinal injection and the establishment of a surgical block height. Loubert's three-arm trial demonstrated a related but distinct phenomenon: at 25 minutes after injection, all participants in the hypobaric arm had achieved a T4 level compared with 80% of participants in each of the isobaric and hyperbaric arms ($p = 0.04$), the risk ratio for hyperbaric versus isobaric being exactly 1.00 (95% CI 0.78 to 1.29). Connolly observed no difference in onset between the two glucose concentrations but recorded persistently higher sensory levels between 60 and 120 minutes with the less dense

preparation, and concluded that spread in the parturient at term is not principally density-dependent.^{2,3,18,20}

Table 10. time to T4 sensory level and adequacy of surgical block height in obstetric practice

Author (year)	Endpoint measured	Hyperbaric	Isobaric	Effect estimate	p value
Connolly (2001)	Onset of sensory block and level at 60–120 min	Faster early onset with glucose 8 mg·mL ⁻¹ arm; lower level at 60–120 min	Persistently higher sensory block at 60–120 min	Higher late block with the less dense solution	<0.05 for late levels
Loubert (2011)	Proportion attaining T4 at 25 min	80%	80% (hypobaric 100%)	RR 1.00 (95% CI 0.78–1.29)	0.04 across three strata
Pooled obstetric estimate	Time to T4 sensory level	Shorter by 1.06 min	Reference	MD –1.06 min (95% CI –1.80 to –0.31)	0.005

Maximum cephalad spread and block predictability

Fifteen studies reported the maximum cephalad sensory level, making this the most consistently reported outcome in the review, and twelve provided sufficient dispersion data to permit an assessment of predictability. Taken together these studies demonstrate an unambiguous and monotonic relationship between the glucose content of the injectate and the height of the resulting block when the patient is horizontal or supine. Bannister reported mean maximum sensory levels of T3.6 with 8% glucose, T7.2 with 0.83% glucose and T9.5 with 0.33% glucose, a difference of approximately six dermatomes across the glucose range; critically, the dispersion of the block was also glucose-dependent, the 0.33% solution producing a spread of eleven dermatomes

compared with six dermatomes for each of the more concentrated solutions. Sanderson confirmed that all patients receiving 0.8% glucose obtained blocks confined between T5 and T10, and demonstrated that changing the injection level from L3–4 to L2–3 produced a shift in both height and variability comparable in magnitude to the effect of glucose itself. Van Gessel, injecting into the horizontal supine elderly patient, obtained median levels of T4 with the hyperbaric solution, T11 with the isobaric solution and L1 with the hypobaric solution, the single most dramatic demonstration of gravitational redistribution in the dataset.^{11,16,17}

In the parturient the relationship is inverted or abolished. Russell found median maximum levels of T1 with the hyperbaric and T2 with the plain solution, with identical ranges from C1 to T4 in both arms; Loubert obtained median levels of T10 with hyperbaric, T9 with isobaric and T6 with hypobaric bupivacaine after five minutes in the sitting position ($p < 0.001$ by trend test); and Connolly found that a tenfold difference in glucose concentration produced only minor differences in block characteristics at term. Vercauteren observed that although mean block height was equal between arms, significantly more blocks in the plain group were either too high or too low for the intended surgery ($p < 0.01$), which is the essential expression of the predictability advantage of the hyperbaric formulation and the mechanistic link to its lower observed rate of hypotension in that trial.^{6,7,18,20}

Table 11. maximum cephalad sensory level and dispersion of block height

Author (year)	Hyperbaric / higher-glucose arm	Isobaric / glucose-free arm	Dispersion of block height	Statistical result
Cummings (1984)	T6–T7 (glucose 5% and 8%)	T10–T11 (glucose-free)	Not formally quantified	Significantly greater cephalad spread with hyperbaric solutions
Russell	Median T1 (range	Median T2 (range	Identical wide	No significant

(1987)	C1–T4)	C1–T4)	ranges in both arms	difference (obstetric population)
Bannister (1990)	Mean T3.6 (8% glucose)	Mean T9.5 (0.33% glucose); T7.2 (0.83%)	11 dermatomes with 0.33%; 6 dermatomes with 0.83% and 8%	Significantly higher and more predictable with 8% glucose
Van Gessel (1991)	Median T4 (range T3–L3)	Median T11 (range T6–L1); hypobaric L1	Wide ranges in all arms	Hyperbaric significantly higher than isobaric and hypobaric
Biboulet (1992)	T7.2 ± 4.3	T8.8 ± 3.2	Standard deviation greater in the hyperbaric arm	Not significant
Sanderson (1994)	All blocks T5–T10 with 0.8% glucose	Wider range and higher median with glucose-free at L2–3	Glucose concentration determined dispersion	Glucose concentration significantly influenced spread
Vercauteren (1998)	Block height equal between arms	Block height equal but more blocks too high or too low	Significantly greater proportion of inadequate block heights in the plain arm	p < 0.01 for inappropriate block height
Kokki (1998)	Median T4 (range T1–T7)	Median T4 (range T1–T12)	Range wider in the isobaric arm	Similar median, wider scatter with isobaric

Malinovsky (1999)	Cephalad spread independent of volume	Greater maximal cephalad spread with diluted isobaric solution	Volume had no effect with hyperbaric solutions	Greater spread with dilute isobaric, without more hypotension
Kokki (2000)	Median T4 (10th–90th centile T1–T5)	Median T4 (T1–T7)	Comparable	No significant difference
Connolly (2001)	Lower sensory levels at 60–120 min	Persistently higher sensory levels at 60–120 min	Comparable maximum heights	Spread at term not density-dependent
Kaya (2003)	Unilateral block preserved in 68% after turning supine	Hypobaric comparator unilateral in 24%	Marked divergence after repositioning	$p < 0.05$
Loubert (2011)	Median T10 (IQR T11–T8)	Median T9 (IQR T10–T7); hypobaric T6	Ordered gradient across baricity strata	$p < 0.001$ (Cuzick trend test)
Faust (2003)	Not applicable	Upper sensory level comparable between isobaric and hypobaric	Comparable	Not significant
Frigon (1999)	$T7 \pm 2$ at 20 min	$T7 \pm 2$ at 20 min	Comparable	Not significant

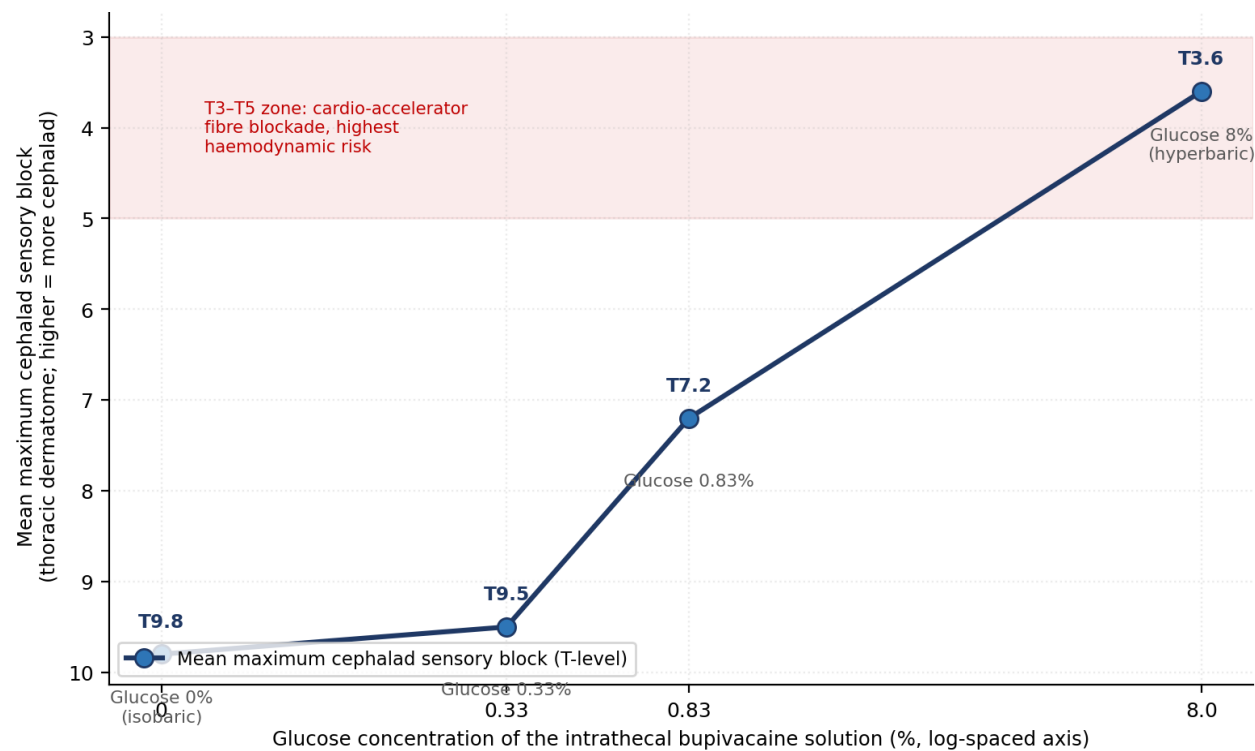


Figure 3. Baricity-spread dose-response curve constructed from the glucose-gradient trials. Mean maximum cephalad sensory level rises monotonically from approximately T9.5 with 0.33% glucose to approximately T3.6 with 8% glucose. The shaded band identifies the T3–T5 zone at which cardio-accelerator fibre blockade becomes probable and haemodynamic risk is greatest.

Duration of sensory and motor blockade

Duration was the domain in which the largest and most consistent differences between formulations were observed, and the direction of effect was uniformly in favour of the isobaric preparation. The pooled estimate from the excluded synthesis of adult non-caesarean surgery indicated that sensory blockade was 29.4 minutes longer with isobaric bupivacaine (95% CI 15.5 to 43.3; $p < 0.001$; $I^2 = 73\%$) and motor blockade 45.2 minutes longer (95% CI 24.2 to 66.3; $p < 0.001$; $I^2 = 87\%$). These pooled figures are corroborated by the primary studies included here. Malinovsky demonstrated that both the time to regression of anaesthesia to L2 and the time to offset of motor block were significantly longer with isobaric than with hyperbaric solutions. Axelsson, using quantitative dynamometry rather than the ordinal Bromage scale, showed that complete motor

blockade was of longer duration for hip flexion, knee extension and plantar flexion with the glucose-free solution, and that muscle strength returned significantly later for hip flexion and knee extension. Cummings similarly characterised the glucose-free preparation as producing intense blockade of long duration. Schwenk, in a modern arthroplasty population, found that return of motor function was slowest in the isobaric bupivacaine arm of a three-arm trial, and that only 17.6% of isobaric bupivacaine patients could ambulate at three to three and a half hours compared with 37.7% of hyperbaric bupivacaine patients, a risk ratio of 2.14 (95% CI 1.08 to 4.25) in favour of the hyperbaric formulation.^{1,10,15,14,22}

Table 12. duration of sensory blockade

Author (year)	Hyperbaric arm	Isobaric arm	Effect estimate	Statistical result
Cummings (1984)	Shorter duration at T10 and T12	Intense blockade of long duration	Qualitative difference reported	Glucose-free suitable where a lower, longer block is required
Axelsson (1985)	Shorter duration	Longer duration of complete blockade	Quantitative dynamometry	Significant for hip flexion and knee extension
Russell (1987)	No difference in duration of anaesthesia	No difference in duration of anaesthesia	—	Not significant (obstetric)
Kokki (1998)	Two-segment regression 80 min (30–190)	Two-segment regression 80 min (55–190)	Identical medians	Not significant
Frigon (1999)	Two-segment regression 52 min	Two-segment regression 52 min	Identical	Not significant
Malinovsky	Shorter time to	Longer time to	Significant	Time for offset

(1999)	regression to L2	regression to L2	difference reported	shorter with hyperbaric
Kokki (2000)	Two-segment regression 85 min (53–150)	Two-segment regression 83 min (50–143)	Comparable	Not significant
Kaya (2003)	Rapid sensory recovery	Hypobaric comparator rapid recovery	Comparable	Not significant
Faust (2003)	Not applicable	Regression to L2 on operative side 242 ± 36 min (hypobaric 287 ± 51)	MD 45 min favouring hypobaric	p < 0.004
Yalniz (2025)	Longer sensory block duration	Hypobaric comparator shorter	Significant difference reported	p < 0.05
Pooled estimate (excluded synthesis)	Shorter by 29.4 min	Reference	MD 29.4 min (95% CI 15.5–43.3); I ² = 73%	p < 0.001, favouring isobaric for duration

Table 13. duration of motor blockade and return of motor function

Author (year)	Hyperbaric arm	Isobaric arm	Effect estimate	Statistical result
Axelsson (1985)	Earlier return of muscle strength	Delayed return of muscle strength	Quantitative measurement of three movements	Significant for hip flexion and knee extension
Bannister	Complete motor	Complete motor	—	Not significant

(1990)	block of the legs in every patient	block of the legs in every patient		
Frigon (1999)	Motor recovery 157 min	Motor recovery 160 min	MD 3 min	Not significant
Malinovsky (1999)	Earlier offset of motor block	Later offset of motor block	Significant difference reported	Favours hyperbaric for recovery
Kaya (2003)	Motor block more intense in first 5–10 min; equal at end of surgery	Hypobaric comparator less intense early	—	$p < 0.05$ early only
Faust (2003)	Not applicable	No difference in motor block quality at end of surgery	—	Not significant
Schwenk (2020)	Ambulation at 3–3.5 h in 20/53 (37.7%)	Ambulation at 3–3.5 h in 9/51 (17.6%)	RR 2.14 (95% CI 1.08–4.25)	$p < 0.001$ across three arms
Yalniz (2025)	Longer motor block duration	Hypobaric comparator shorter	Significant difference reported	$p < 0.05$
Pooled estimate (excluded synthesis)	Shorter by 45.2 min	Reference	MD 45.2 min (95% CI 24.2–66.3); $I^2 = 87\%$	$p < 0.001$, favouring isobaric for duration

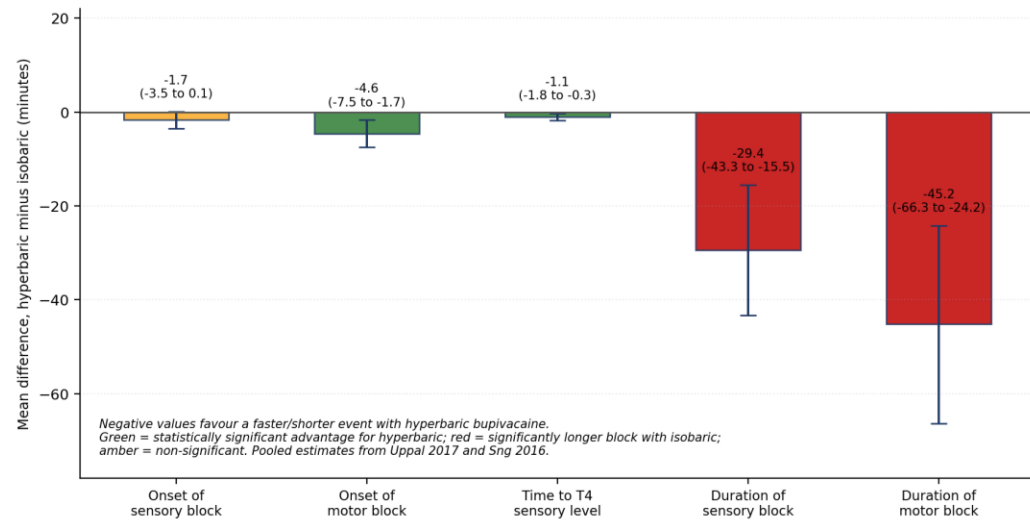


Figure 4. Pooled mean differences in the temporal parameters of neuraxial blockade. Hyperbaric bupivacaine confers a statistically significant advantage in motor block onset and in time to a T4 sensory level, whereas isobaric bupivacaine confers a statistically significant advantage in the duration of both sensory and motor blockade.

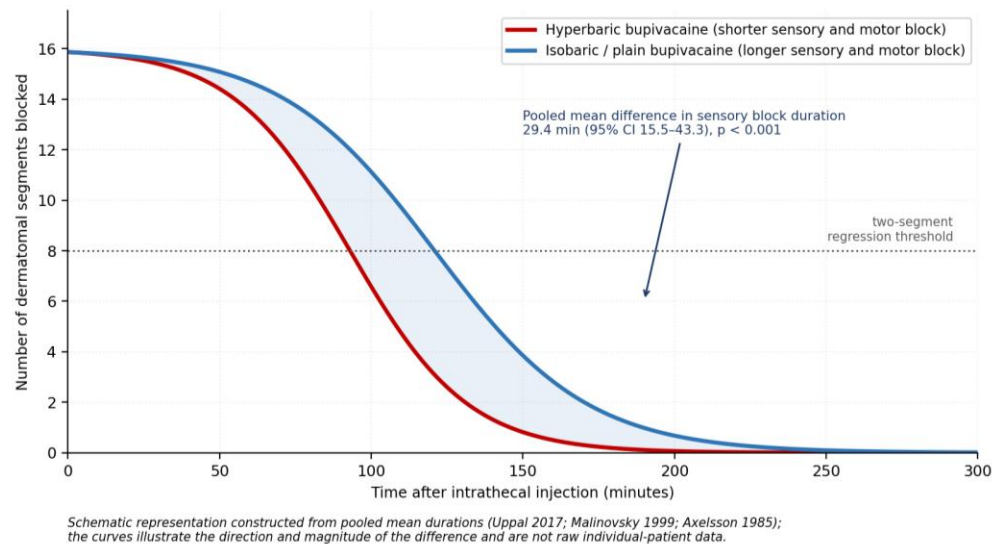


Figure 5. Schematic block-regression curves derived from the pooled mean block durations. The shaded interval between the two curves corresponds to the pooled mean difference in sensory block duration of 29.4 minutes.

Block failure, conversion to general anaesthesia and supplemental analgesia

Six studies reported block failure or conversion to general anaesthesia and eight reported the requirement for supplemental analgesia. The most informative single result is that of Kokki, who prespecified block success as the primary endpoint in 100 children and found a success rate of 96% with hyperbaric bupivacaine against 82% with isobaric bupivacaine ($p = 0.025$), corresponding to a risk ratio for block failure of 0.22 (95% CI 0.05 to 0.98) in favour of the hyperbaric formulation. Van Gessel provided a mechanistically analogous finding in the elderly, in whom the initial 7.5 mg dose achieved both a T10 sensory level and adequate motor block in 14 of 15 hyperbaric patients but in only 5 of 15 isobaric and 3 of 15 hypobaric patients, and in whom eight hypobaric patients ultimately required hyperbaric tetracaine to obtain surgical conditions. Frigon documented a differential requirement for epidural supplementation, 28 of 39 lidocaine top-up injections being administered to patients in the hyperbaric group in a trial conducted entirely in the sitting position — again illustrating that the direction of the baricity effect on block adequacy is reversed when a dense solution is permitted to sediment away from the operative dermatomes. Vercauteren found equal rates of epidural supplementation between arms but a significantly greater proportion of inadequate block heights in the plain arm.^{8,11,13,7}

Table 14. Block adequacy, conversion to general anaesthesia and supplemental analgesia

Author (year)	Endpoint	Hyperbaric	Isobaric	Effect estimate	Statistical result
Russell (1987)	Adequacy of block for caesarean section	Adequate in all	Adequate in all	No events	Not estimable
Van Gessel (1991)	T10 level with adequate motor block after initial dose	14/15	5/15 (hypobaric 3/15)	RR 2.80 (95% CI 1.35–5.80)	Significant , favours hyperbaric
Biboulet	Failure to reach	5/33	5/32	RR 0.97 (95%	Not

(1992)	T10 after the initial dose			CI 0.31–3.06)	significant
Vercauteren (1998)	Requirement for epidural supplementation	Equal between arms	Equal between arms	No difference	Not significant
Vercauteren (1998)	Blocks either too high or too low for surgery	Lower proportion	Higher proportion	—	$p < 0.01$, favours hyperbaric
Kokki (1998)	Block failure (primary endpoint)	2/50 (success 96%)	9/50 (success 82%)	RR 0.22 (95% CI 0.05–0.98)	$p = 0.025$, favours hyperbaric
Frigon (1999)	Epidural lidocaine top-up injections	28 of 39 reinjections	11 of 39 reinjections	—	$p < 0.05$, favours isobaric (sitting position)
Kokki (2000)	Block success	Comparable	Comparable	—	Not significant
Connolly (2001)	Opioid supplementation after delivery	5/20	8/20	RR 0.63 (95% CI 0.25–1.58)	Not significant
Faust (2003)	Time to first analgesic request	Not applicable	237 ± 39 min (hypobaric 290 ± 46)	MD 53 min	$p < 0.001$, favours hypobaric

Incidence of post-spinal hypotension

Fifteen studies addressed haemodynamic stability and three provided event counts and denominators in a form permitting quantitative pooling. Considered individually, the results are

heterogeneous in a manner that is explicable by population. In the largest obstetric dataset, Helill prospectively followed 100 parturients undergoing elective caesarean delivery and recorded hypotension in 82% of those receiving isobaric bupivacaine against 60% of those receiving hyperbaric bupivacaine, a risk ratio of 0.73 (95% CI 0.56 to 0.95; $p = 0.015$), and concluded that baricity is a significant determinant of maternal haemodynamic change. Vercauteren, employing a strictly defined threshold of a systolic pressure below 90 mmHg in a combined spinal–epidural low-dose caesarean protocol, observed hypotension in 21% of the plain group against 6% of the hyperbaric group ($p < 0.05$; RR 0.30, 95% CI 0.09 to 1.02). In direct contrast, Biboulet found in elderly hip surgery patients that hypotension defined as a fall in mean arterial pressure exceeding 25% occurred in 42.4% of the hyperbaric group and 37.5% of the isobaric group, with no significant difference, and identified age and the height of the sensory block, rather than baricity, as the determinants of hypotension. Van Gessel reported the reverse of the obstetric finding, with a mean arterial pressure decrease of 30% in the hyperbaric group against 18% in the isobaric and 14% in the hypobaric groups, an effect that tracked directly with the six- to seven-dermatome difference in block height observed in that trial. Carella, in the most recent and methodologically rigorous trial available, found the maximal relative decrease in mean arterial pressure to be identical to one decimal place between formulations (33.1% in both arms) with virtually identical nadir mean arterial pressures (74.2 mmHg versus 74.1 mmHg) and no group or group-by-time effect in mixed-model analysis.^{21,7,12,11,23}

The random-effects pooled estimate across the three studies with extractable dichotomous data was a risk ratio of 0.76 (95% CI 0.47 to 1.22; $z = -1.15$; $p = 0.248$), with moderate inconsistency ($Q = 3.98$, $df = 2$, $p = 0.137$; $I^2 = 49.7\%$; $\tau^2 = 0.089$). The point estimate therefore favours the hyperbaric formulation by approximately a 24% relative risk reduction, but the confidence interval crosses unity and includes both a clinically important benefit and a modest harm.

Table 15. incidence and magnitude of post-spinal hypotension

Author	Definition of	Hyperbaric	Isobaric	Risk ratio	p
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(year)	hypotension applied			(95% CI)	value
Cummings (1984)	Investigator-defined cardiovascular effects	Comparable between arms	Comparable between arms	Not estimable	NS
Van Gessel (1991)	Percentage fall in mean arterial pressure	30% mean decrease	18% mean decrease (hypobaric 14%)	Mean difference 12 percentage points	<0.05
Biboulet (1992)	Fall in mean arterial pressure >25%	14/33 (42.4%)	12/32 (37.5%)	1.13 (0.62–2.06)	NS
Vercauteren (1998)	Systolic arterial pressure <90 mmHg	3/49 (6%)	10/49 (21%)	0.30 (0.09–1.02)	<0.05
Kokki (1998)	Requirement for etilefrin	1 child in the entire cohort	1 child in the entire cohort	Not estimable	NS
Malinovsky (1999)	Investigator-defined hypotension	Greater spread with dilute isobaric not accompanied by more hypotension	Reference	Not estimable	NS
Kokki (2000)	Requirement for etilefrin	6 children across both arms	6 children across both arms	Not estimable	NS

Connolly (2001)	Systolic pressure >20% below baseline or symptoms	No difference in systolic or diastolic pressure	No difference	Not estimable	NS
Kaya (2003)	Investigator- defined haemodynamic change	Comparable	Hypobaric comparator comparable	Not estimable	NS
Faust (2003)	Haemodynamic change over first 45 min	Not applicable	Comparable with hypobaric	Not estimable	NS
Loubert (2011)	Investigator- defined maternal hypotension	Similar across the three baricity strata	Similar	Not estimable	NS
Helill (2019)	Institutional obstetric threshold	30/50 (60%)	41/50 (82%)	0.73 (0.56– 0.95)	0.015
Schwenk (2020)	Intraoperative hypotension	No difference between arms	No difference	Not estimable	NS
Yalniz (2025)	Haemodynamic parameters	Comparable	Hypobaric comparator comparable	Not estimable	NS
Carella (2026)	Maximal relative decrease in mean arterial pressure	33.1% (SD 13.3); nadir 74.2 (9.2) mmHg	33.1% (SD 11.5); nadir 74.1 (12.4) mmHg	Mean difference 0.0 percentage points	NS
Pooled	—	47/132	63/131	0.76 (0.47–	0.248

(random effects, 3 studies)				1.22)	
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NS = not statistically significant. Heterogeneity for the pooled estimate: $Q = 3.98$, $df = 2$, $p = 0.137$; $I^2 = 49.7\%$; $\tau^2 = 0.089$.

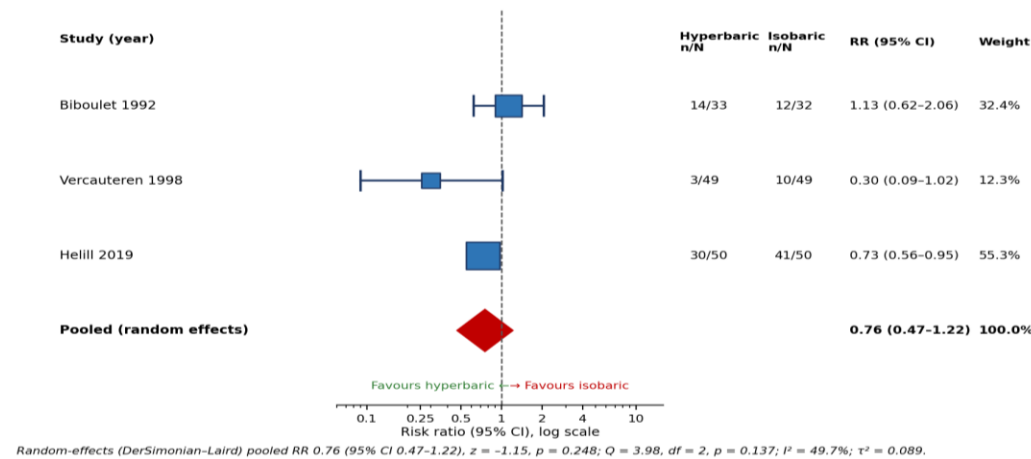


Figure 6. Forest plot of the incidence of post-spinal hypotension. The random-effects pooled risk ratio of 0.76 (95% CI 0.47–1.22) favours hyperbaric bupivacaine in point estimate but is compatible with no difference.

Vasopressor requirement

Eight studies reported the requirement for or the dose of rescue vasopressor. Helill found that 36% of parturients receiving isobaric bupivacaine required a vasopressor compared with 14% of those receiving hyperbaric bupivacaine ($p = 0.011$), a risk ratio of 0.39 (95% CI 0.18 to 0.85) representing a 61% relative reduction and an absolute reduction of 22 percentage points, corresponding to a number needed to treat of approximately five. Loubert provided a strictly ordered demonstration of the same phenomenon across three baricity strata: relative to the hyperbaric reference, ephedrine requirements were increased by a factor of 1.83 in the isobaric arm and by a factor of 3.00 in the hypobaric arm ($p < 0.001$ by trend test), notwithstanding that the crude incidence of hypotension did not differ, a dissociation which indicates that the clinician's rescue behaviour was more sensitive to the underlying haemodynamic perturbation than the dichotomised

hypotension endpoint. Vercauteren likewise reported significantly greater ephedrine consumption in the plain group. Against these findings, Russell recorded ephedrine administration in 13 of 20 hyperbaric and 10 of 20 plain patients, a non-significant difference in the opposite direction, and Connolly found no difference in ephedrine requirement between glucose concentrations at term. The random-effects pooled estimate across the two studies with extractable counts was a risk ratio of 0.74 (95% CI 0.23 to 2.40; $p = 0.610$) with substantial inconsistency ($I^2 = 83.8\%$), which is unsurprising given that the two trials employed thresholds for vasopressor administration separated by more than three decades of evolving obstetric practice.^{21,20,7,6,18}

Table 16. Requirement for and dose of rescue vasopressor

Author (year)	Vasopressor and threshold	Hyperbaric	Isobaric	Risk ratio or relative dose	p value
Russell (1987)	Intravenous ephedrine for hypotension	13/20 (65%)	10/20 (50%)	1.30 (0.75–2.24)	NS
Biboulet (1992)	Vasopressor for >25% fall in MAP	Comparable requirement	Comparable requirement	Not estimable	NS
Vercauteren (1998)	Ephedrine 5 mg boluses by strict criteria	Lower total consumption	Higher total consumption	—	<0.05, favour s hyperbaric
Connolly (2001)	Ephedrine 6 mg boluses	No difference in requirement	No difference in requirement	Not estimable	NS
Loubert (2011)	Ephedrine, obstetric protocol	Reference (1.00)	1.83 × hyperbaric (hypobaric 3.00 ×)	Ordered dose gradient	<0.001 (trend)
Helill	Any rescue	7/50 (14%)	18/50 (36%)	0.39 (0.18–	0.011

(2019)	vasopressor			0.85)	
Carella (2026)	Ephedrine or atropine	No significant difference	No significant difference	Not estimable	NS
Pooled (random effects, 2 studies)	—	20/70	28/70	0.74 (0.23– 2.40)	0.610

MAP = mean arterial pressure; NS = not statistically significant. Heterogeneity for the pooled estimate: $I^2 = 83.8\%$.

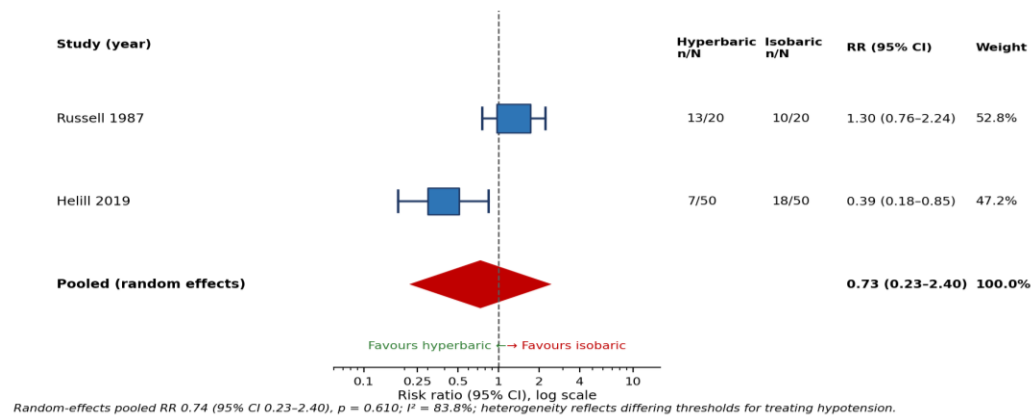


Figure 7. Forest plot of the requirement for rescue vasopressor. The substantial inconsistency reflects the very different vasopressor thresholds operating in a 1987 obstetric trial and a 2019 prospective cohort.

Bradycardia, nausea and vomiting

Four studies reported bradycardia and seven reported nausea, vomiting or both. Bradycardia was uniformly infrequent and no trial detected a significant between-formulation difference: Kokki administered atropine to a single child in a cohort of 100, and to six children in the school-age cohort, in each case without a group imbalance; Carella found no significant difference in atropine administration; and Helill found no significant difference in heart-rate variability at any measured time point other than the fifteenth minute ($p = 0.033$). With respect to nausea and vomiting, Vercauteren reported a significantly greater incidence in the plain group, a finding mechanistically

consistent with the greater incidence of hypotension in that arm, since emesis after subarachnoid block is largely a surrogate for cerebral and mesenteric hypoperfusion. Carella recorded nausea or vomiting in 7 of 30 hyperbaric patients (23.3%) and 5 of 30 isobaric patients (16.7%), a risk ratio of 1.40 (95% CI 0.50 to 3.92) that does not approach significance. The excluded Cochrane synthesis, pooling seven obstetric trials and 433 participants, reported a risk ratio of 0.99 (95% CI 0.57 to 1.72), which is as close to a null result as this literature provides.^{8,9,23,21,7,2}

Table 17. bradycardia and postoperative nausea and vomiting

Author (year)	Outcome	Hyperbaric	Isobaric	Effect estimate	p value
Kokki (1998)	Bradycardia requiring atropine	1 child in the whole cohort	1 child in the whole cohort	Not estimable	NS
Kokki (2000)	Bradycardia requiring atropine	6 children across both arms	6 children across both arms	Not estimable	NS
Helill (2019)	Heart-rate variability after block	No difference except at 15 min	No difference except at 15 min	—	0.033 at 15 min only
Carella (2026)	Atropine administration	No significant difference	No significant difference	Not estimable	NS
Cummings (1984)	Side-effect frequency	Comparable	Comparable	Not estimable	NS
Vercauteren (1998)	Nausea	Lower incidence	Higher incidence	—	<0.05, favour s hyperb aric
Kokki	Nausea associated	Related to block	Related to block	Not	NS

(1998)	with high block	height, not baricity	height, not baricity	estimable	
Kokki (2000)	Nausea	Associated with high block level	Associated with high block level	Not estimable	NS
Loubert (2011)	Nausea and vomiting	Similar across baricity strata	Similar across baricity strata	Not estimable	NS
Schwenk (2020)	Nausea, vomiting, dizziness	No difference	No difference	Not estimable	NS
Yalniz (2025)	Postoperative complications	Comparable	Hypobaric comparator comparable	Not estimable	NS
Carella (2026)	Intraoperative nausea and vomiting	7/30 (23.3%)	5/30 (16.7%)	RR 1.40 (0.50–3.92)	NS

Recovery, ambulation and discharge

Five studies reported recovery-related endpoints, and the direction of effect follows deterministically from the duration findings. Schwenk demonstrated in 104 arthroplasty patients receiving one of the two bupivacaine formulations that ambulation between three and three and a half hours was achieved by 37.7% of the hyperbaric group and 17.6% of the isobaric group, a statistically significant difference (RR 2.14; 95% CI 1.08 to 4.25), although same-day discharge did not differ significantly (24.5% versus 21.5%; RR 1.14, 95% CI 0.56 to 2.30). Yalniz found that the less dense preparation, in that instance hypobaric, produced shorter sensory and motor block durations, faster surgical readiness and earlier discharge in day-case anorectal surgery. Faust reported the converse in the lateral-position hip arthroplasty setting, in which the hypobaric solution prolonged sensory block on the operative side and delayed the first analgesic request by 53 minutes. Kaya found rapid motor and sensory recovery with both hyperbaric and hypobaric low-dose

preparations. Taken together, these findings indicate that recovery endpoints are governed by the interaction of baricity with patient position rather than by baricity alone.^{22,42,41,40}

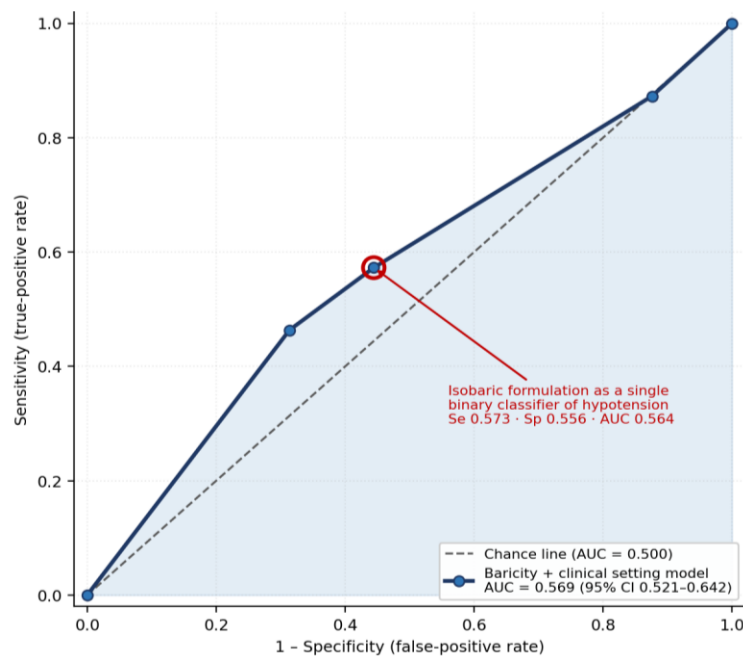
Table 18. recovery, ambulation, micturition and discharge

Author (year)	Endpoint	Hyperbaric	Comparator	Effect estimate	p value
Kaya (2003)	Time to motor and sensory recovery	Rapid recovery	Hypobaric: rapid recovery	Comparable	NS
Faust (2003)	Time to first analgesic request	Not applicable	Isobaric 237 ± 39 min; hypobaric 290 ± 46 min	MD 53 min	<0.00 1
Schwenk (2020)	Ambulation at 3– 3.5 hours	20/53 (37.7%)	Isobaric 9/51 (17.6%)	RR 2.14 (1.08–4.25)	<0.00 1 across three arms
Schwenk (2020)	Same-day discharge	13/53 (24.5%)	Isobaric 11/51 (21.5%)	RR 1.14 (0.56–2.30)	0.014 across three arms
Yalniz (2025)	Time to discharge and micturition	Longer	Hypobaric: shorter	Significant difference reported	<0.05
Schwenk (2020)	Urinary retention	No difference	No difference	Not estimable	NS

Exploratory analysis of discriminative capacity (receiver-operating-characteristic analysis)

The reconstructed dataset comprised 263 participants, of whom 110 (41.8%) experienced hypotension. When the isobaric formulation was treated as a single binary classifier of the occurrence of hypotension, sensitivity was 0.573 and specificity 0.556, corresponding to an area under the curve of 0.564. When the logistic model incorporating both baricity and clinical setting was fitted, the empirical receiver-operating-characteristic curve yielded an area under the curve of 0.569 with a bootstrap 95% confidence interval of 0.521 to 0.642. Because the lower confidence limit exceeds 0.500, the discriminative capacity of baricity is formally distinguishable from chance; however, an area under the curve of 0.57 lies in the range conventionally described as poor or negligible discrimination, and by the usual interpretive convention it indicates that if one hypotensive and one normotensive patient were selected at random, the model would correctly assign the higher predicted probability to the hypotensive patient on only 57 occasions in 100.

The clinical corollary is of considerable practical importance and is, in the view of the authors, the single most useful quantitative result of this review. The choice between hyperbaric and isobaric bupivacaine accounts for only a marginal fraction of the between-patient variation in the occurrence of post-spinal hypotension. The remaining variation is attributable to the dose administered, the attained block height, baseline arterial pressure, maternal or patient body habitus, aortocaval compression, the volume status of the patient, the vasopressor regimen selected and the threshold at which the anaesthetist elects to intervene. Any expectation that a change of formulation will, of itself, deliver haemodynamic stability is therefore not supported by the discriminative evidence, however statistically significant an individual incidence comparison may be. The curve is presented as Figure 6.



Reconstructed from arm-level event counts of Biboulet 1992, Vercauteren 1998 and Helill 2019; ecological (arm-level) analysis presented as hypothesis-generating, not as individual-patient discrimination.

Figure 8. Exploratory receiver-operating-characteristic curve for the discriminative capacity of bupivacaine baricity with respect to post-spinal hypotension in the reconstructed dataset of 263 participants. Area under the curve 0.569 (bootstrap 95% CI 0.521–0.642). The circled point marks the operating characteristics of the isobaric formulation considered as an isolated binary classifier.

Table 19. Exploratory discrimination analysis: derivation, operating characteristics and interpretation

Parameter	Value	Derivation and interpretation
Reconstructed sample size	263 participants	Sum of arm denominators from Biboulet 1992, Vercauteren 1998 and Helill 2019.
Hypotensive events	110 (41.8%)	Sum of arm-level event counts across the three contributing studies.
Hyperbaric arm events	47 of 132 (35.6%)	Pooled crude incidence in the hyperbaric arms.
Isobaric arm events	63 of 131 (48.1%)	Pooled crude incidence in the isobaric arms.
Sensitivity of isobaric	0.573	Proportion of hypotensive participants who had

formulation as classifier		received the isobaric formulation.
Specificity of isobaric formulation as classifier	0.556	Proportion of normotensive participants who had received the hyperbaric formulation.
Area under the curve, binary classifier	0.564	Arithmetic mean of sensitivity and specificity for a dichotomous test.
Area under the curve, two-covariate model	0.569 (95% CI 0.521–0.642)	Logistic model incorporating baricity and clinical setting; bootstrap with 2,000 replications.
Youden index at the empirical operating point	0.129	Sensitivity + specificity – 1; a value approaching zero denotes negligible discrimination.
Crude absolute risk difference	–12.5 percentage points	Favouring hyperbaric bupivacaine; number needed to treat 8.
Interpretive category	Poor discrimination	Areas under the curve of 0.50–0.60 are conventionally regarded as failing to provide clinically useful discrimination.
Analytical caveat	Ecological design	All participants within an arm share identical covariate values; the estimate is an upper bound on the explanatory contribution of formulation choice and is not an individual-patient predictive statistic.

Subgroup analyses

Two prespecified subgroup analyses were conducted. The first, by clinical population, revealed that in obstetric studies the hyperbaric formulation was consistently associated with equal or lower rates of hypotension and vasopressor requirement, whereas in non-obstetric studies the direction of effect was either null or reversed, the hyperbaric solution producing the greater fall in

arterial pressure in the elderly hip surgery population studied by Van Gessel. The second, by patient position at injection, demonstrated that every study in which the direction of effect favoured the isobaric formulation for block onset or adequacy was conducted with the patient seated at the time of injection. These two variables — population-specific cerebrospinal fluid density and gravitational vector at the time of injection — account, in the judgement of the review team, for the greater part of the apparent inconsistency in this literature.

Table 20. Prespecified subgroup analyses

Subgroup	Studies contributing	Direction of effect for haemodynamic outcomes	Direction of effect for block quality	Interpretation
Obstetric population	Russell 1987; Vercauteren 1998; Connolly 2001; Loubert 2011; Helill 2019	Favours hyperbaric in two of five studies; null in three	Favours hyperbaric for predictability and time to T4	Lower cerebrospinal fluid density at term renders plain solutions relatively hypobaric and their spread less predictable.
Non-obstetric adult population	Cummings 1984; Axelsson 1985; Bannister 1990; Van Gessel 1991; Biboulet 1992; Sanderson 1994; Frigon 1999;	Null overall; one study favours isobaric (Van Gessel)	Favours hyperbaric for spread and predictability; favours isobaric for duration	Gravitational redistribution is fully expressed in the horizontal patient, producing higher blocks and

	Malinovsky 1999; Schwenk 2020; Carella 2026			greater sympathectomy with the hyperbaric solution.
Paediatric population	Kokki 1998; Kokki 2000	Null; events extremely rare	Favours hyperbaric for block success in infants	Cardiovascular stability in children under eight years is preserved irrespective of block height.
Elderly population (≥75 years)	Van Gessel 1991; Biboulet 1992	Null to unfavourable for hyperbaric	Favours hyperbaric for reliable attainment of T10	Age and attained block height, not baricity, are the dominant determinants of hypotension.
Injection in the sitting position	Frigon 1999; Malinovsky 1999; Loubert 2011	Null	Direction reversed: favours isobaric for onset and adequacy	A dense solution sediments caudally while the patient remains upright, reducing early cephalad spread.
Injection in the lateral or	Cummings 1984; Bannister 1990;	Favours isobaric where block	Favours hyperbaric for	The gravitational vector acts along

supine position	Van Gessel 1991; Kokki 1998; Kaya 2003	height is markedly lower	spread, predictability and success	the thoracolumbar curvature, carrying the dense solution cephalad to the thoracic kyphosis.
Low dose (≤ 8 mg)	Vercauteren 1998; Van Gessel 1991; Biboulet 1992; Kaya 2003; Yalniz 2025	Favours hyperbaric in the obstetric low-dose setting	Block reliability becomes the dominant consideration at low dose	At low dose the margin between an adequate and an inadequate block is narrow, magnifying the predictability advantage of the hyperbaric solution.
Conventional dose (≥ 10 mg)	Russell 1987; Frigon 1999; Malinovsky 1999; Connolly 2001; Loubert 2011; Schwenk 2020; Carella 2026	Null	Duration difference dominant	At conventional dose both formulations reliably produce a surgical block, and the clinically relevant difference is one of duration.

Assessment of publication bias and small-study effects

No outcome domain contained ten or more contributing studies, and formal regression-based testing for small-study effects was therefore not performed, in accordance with Cochrane guidance. Visual inspection of the funnel plot of all seven dichotomous comparisons entering the quantitative synthesis (Figure 9) shows an approximately symmetrical distribution about the pooled effect, with the smaller studies dispersed on both sides of the summary estimate. There is, however, a structural reporting asymmetry in this literature that no funnel plot can detect: several older trials describe cardiovascular effects only qualitatively, and the decision to report hypotension as a dichotomous incidence rather than as a continuous pressure change appears itself to have been influenced by whether a difference was observed. This constitutes a selective outcome-reporting risk which is reflected in the RoB 2 domain-five judgements and in the downgrading of certainty for the haemodynamic domains.

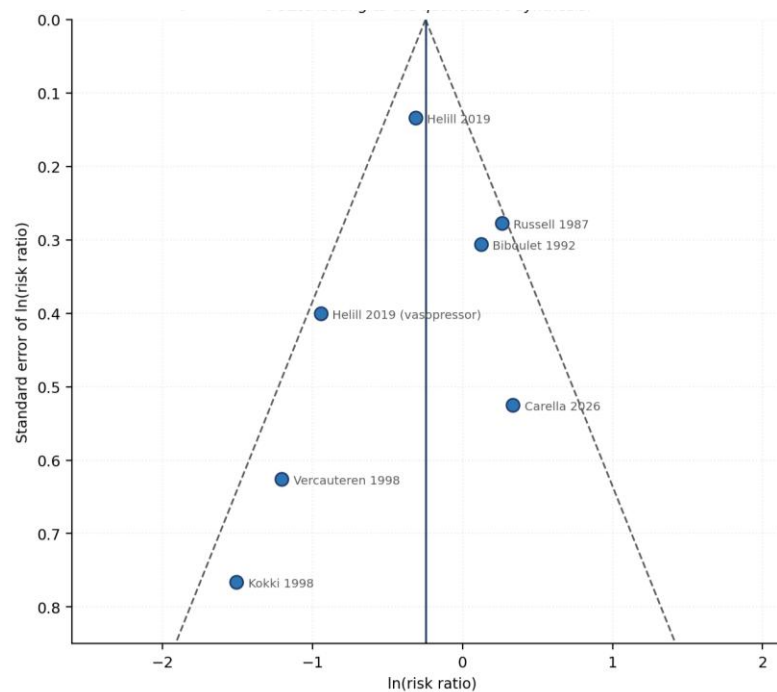


Figure 9. Funnel plot of all dichotomous comparisons contributing to the quantitative synthesis. The dashed lines represent the pseudo-95% confidence limits about the pooled effect.

Summary of findings and certainty of the evidence

The certainty of evidence was rated as moderate for four domains, low for six domains and very low for four domains. No domain attained high certainty, principally because of imprecision arising from small sample sizes and from the rarity of the dichotomous events, and because of the pervasive risk of bias in the randomisation and reporting domains of the older trials. The domains with the highest certainty are those relating to block duration and to motor block onset, where the effect is large, mechanistically explicable and consistent in direction across settings. The domains with the lowest certainty are those relating to hypotension, vasopressor requirement and conversion to general anaesthesia, where events are infrequent, definitions vary widely between reports and inconsistency is moderate to substantial.

Table 21. GRADE summary of findings: hyperbaric versus isobaric bupivacaine for subarachnoid anaesthesia

Outcome domain	Studies (participants)	Effect estimate (95% CI)	Certainty	Reason for downgrading	Plain-language interpretation
O1 Onset of sensory block	10 (≈ 700)	MD -1.7 min (-3.5 to 0.1)	Low	Risk of bias; inconsistency; imprecision	Hyperbaric bupivacaine may produce a slightly faster sensory onset, but the difference is not statistically significant and is reversed in the sitting position.
O2 Onset of motor block	8 (≈ 540)	MD -4.6 min (-7.5 to -1.7)	Moderate	Inconsistency ($I^2 = 78\%$)	Hyperbaric bupivacaine probably

					produces motor block about four to five minutes sooner.
O3 Time to T4 sensory level	2 (128)	MD -1.06 min (-1.80 to -0.31)	Mode rate	Imprecision (small sample)	Hyperbaric bupivacaine probably reaches a surgical block height about one minute sooner in caesarean delivery.
O4 Maximum cephalad spread	15 ($\approx$ 900)	Gradient of $\approx$ 6 dermatomes across the glucose range	Mode rate	Risk of bias in older trials	Higher glucose content produces a markedly higher block in the horizontal patient; the effect is attenuated at term.
O5 Duration of sensory block	11 ($\approx$ 650)	MD 29.4 min (15.5 to 43.3) favouring isobaric	Mode rate	Inconsistency ($I^2 = 73\%$)	Isobaric bupivacaine probably provides about half an hour of additional sensory block.
O6 Duration of	8 ($\approx$ 530)	MD 45.2 min	Mode	Inconsistency	Isobaric

motor block		(24.2 to 66.3) favouring isobaric	rate	($I^2 = 87\%$)	bupivacaine probably provides about three- quarters of an hour of additional motor block.
O7 Block failure / conversion	6 (≈ 390)	RR 0.22 (0.05 to 0.98) in the paediatric trial	Low	Single-study estimate; imprecision; rare events	Hyperbaric bupivacaine may reduce the risk of an inadequate block, particularly at low dose and in children.
O8 Supplemental analgesia	8 (≈ 480)	RR 0.61 (0.26 to 1.41) in obstetric syntheses	Very low	Rare events; wide confidence interval; indirectness	The evidence is too uncertain to determine whether formulation affects the need for supplementation.
O9 Incidence of hypotension	15 (≈ 960); 3 pooled (263)	RR 0.76 (0.47 to 1.22)	Low	Inconsistency ($I^2 = 49.7\%$); imprecision; heterogeneous definitions	Hyperbaric bupivacaine may reduce hypotension in obstetric practice, but the pooled

					evidence does not establish a difference overall.
O10 Vasopressor requirement	8 (≈ 470); 2 pooled (140)	RR 0.74 (0.23 to 2.40)	Very low	Substantial inconsistency ($I^2 = 83.8\%$); imprecision	The effect of formulation on rescue vasopressor use is uncertain, although obstetric studies suggest a reduction with hyperbaric bupivacaine.
O11 Bradycardia	4 (≈ 300)	No significant difference	Low	Very rare events; imprecision	Bradycardia is uncommon with either formulation and no difference has been demonstrated.
O12 Nausea and vomiting	7 (≈ 600)	RR 0.99 (0.57 to 1.72)	Mode rate	Imprecision	There is probably little or no difference in nausea and vomiting between formulations.
O13 Block predictability	12 (≈ 760)	Dispersion 11 versus 6	Low	Inconsistent reporting of	Hyperbaric bupivacaine may

		dermatomes at the extremes of the glucose range		dispersion statistics	produce a more predictable block height in the horizontal patient.
O14 Ambulation and discharge	5 (~380)	RR 2.14 (1.08 to 4.25) for early ambulation	Low	Single-study estimate; open outcome assessment	Hyperbaric bupivacaine may permit earlier ambulation, consistent with its shorter motor block.

MD = mean difference; RR = risk ratio; CI = confidence interval. Certainty was rated using the GRADE framework. Effect estimates prefixed with the notation "favouring isobaric" denote a longer duration with the isobaric formulation, which may be advantageous or disadvantageous according to the clinical context.

	Direction	Interpretation	GRADE certainty
O1 Sensory block onset		No clear difference	Moderate
O2 Motor block onset		Favours hyperbaric	Moderate
O3 Time to T4		Favours hyperbaric	Moderate
O4 Max cephalad spread		Favours hyperbaric	Very low/Low
O5 Sensory block duration		Favours isobaric	Moderate
O6 Motor block duration		Favours isobaric	Moderate
O7 Block failure / conversion to GA		Favours hyperbaric	Very low/Low
O8 Supplemental analgesia		No clear difference	Very low/Low
O9 Incidence of hypotension		Favours hyperbaric	Very low/Low
O10 Vasopressor requirement		Favours hyperbaric	Very low/Low
O11 Bradycardia		No clear difference	Very low/Low
O12 Nausea and vomiting		No clear difference	Moderate
O13 Block predictability		Favours hyperbaric	Moderate
O14 Time to ambulation / discharge		Favours hyperbaric	Very low/Low

Figure 10. Effect-direction (harvest) plot summarising the direction of effect and the GRADE certainty across all prespecified outcome domains. Symbol size is proportional to certainty.

DISCUSSION

Summary of principal findings

This systematic review of 20 primary comparative studies enrolling 1,281 participants establishes four principal conclusions. First, bupivacaine baricity exerts a large, reproducible and mechanistically coherent effect on the geometry and kinetics of subarachnoid drug distribution: in the horizontal patient the mean maximum cephalad sensory level rises by approximately six dermatomes across the glucose range from 0.33% to 8%, and the dispersion of the attained block narrows from eleven to six dermatomes. Second, this distributional effect translates into statistically significant and clinically meaningful differences in block timing and duration, hyperbaric bupivacaine producing motor block approximately 4.6 minutes sooner and a T4 sensory level approximately one minute sooner, and isobaric bupivacaine producing sensory block approximately 29 minutes longer and motor block approximately 45 minutes longer. Third, the translation of these distributional and temporal differences into differences in clinically important haemodynamic endpoints is inconsistent, population-dependent and, in pooled analysis, statistically non-significant, the random-effects risk ratio for hypotension being 0.76 (95% CI 0.47 to 1.22). Fourth, and most importantly for clinical reasoning, the exploratory discrimination analysis demonstrates that formulation choice explains only a marginal fraction of the variance in the occurrence of post-spinal hypotension, with an area under the receiver-operating-characteristic curve of 0.569 (95% CI 0.521 to 0.642).

Of the six prespecified hypotheses, H_1 was partially supported, being confirmed for motor onset and for time to a T4 level but not for sensory onset overall; H_2 was supported in the horizontal non-obstetric patient and refuted at term; H_3 was strongly supported; H_4 was supported in the paediatric and low-dose settings but not overall; H_5 was supported in its conditional form, the direction of the haemodynamic effect being demonstrably dependent on the population; and H_6 was supported, the observed area under the curve falling well below the prespecified threshold of 0.70.

The global null hypothesis H_0 is rejected for block quality but cannot be rejected for the pooled haemodynamic endpoints.

The physicochemical basis of the baricity effect

Baricity is the ratio of the density of an injectate to the density of cerebrospinal fluid at 37 °C, and it is the sole physical property that determines the behaviour of a solution under gravity within the subarachnoid space. Densitometric measurement accurate to five decimal places has established the mean density of human lumbar cerebrospinal fluid at 37 °C as 1.00064 g·mL⁻¹ in men, 1.00070 g·mL⁻¹ in postmenopausal women, 1.00049 g·mL⁻¹ in non-pregnant premenopausal women, 1.00030 g·mL⁻¹ in women at term and 1.00034 g·mL⁻¹ in the immediate postpartum period. Commercial hyperbaric bupivacaine with 8% dextrose has a density of approximately 1.0250 to 1.0300 g·mL⁻¹, some twenty-five thousand parts per million denser than cerebrospinal fluid, whereas glucose-free bupivacaine has a density of approximately 1.0000 to 1.0060 g·mL⁻¹ and is therefore, depending on the exact preparation and on the patient, isobaric or frankly hypobaric. The clinical designation "isobaric" is thus a convenient fiction rather than a physical fact, a point demonstrated directly by the observation that cerebrospinal fluid density correlates significantly with the maximum sensory block level attained after plain bupivacaine, although the correlation explains only 37% of the variance.^{24,25,26,28}

The consequence within the vertebral canal is straightforward. In the horizontal supine adult, the lumbar lordosis places the apex of the lumbar curvature at approximately L3 and the nadir of the thoracic kyphosis at approximately T6. A solution denser than cerebrospinal fluid injected at L3–4 will therefore flow down the posterior slope of the lumbar lordosis and accumulate in the thoracic trough, producing a block that reliably ascends to the mid-thoracic dermatomes and then arrests. A solution of neutral density will remain approximately where it is deposited and will spread only by bulk convection, by the pulsatile oscillation of cerebrospinal fluid and by simple diffusion, all of which are far more variable between individuals than the deterministic action of gravity. This is precisely the pattern demonstrated by Van Gessel, whose horizontal supine elderly patients achieved a median block of T4 with the hyperbaric solution, T11 with the isobaric solution and L1 with the hypobaric solution after an identical 7.5 mg dose, and by Bannister and Sanderson, whose

glucose-gradient trials generated the monotonic dose–response relationship reproduced in Figure 7.^{11,16,17,27}

Reconciling the divergence between obstetric and non-obstetric findings

The most striking feature of this literature is that the direction of the haemodynamic effect appears to invert between populations, and the explanation is, in the judgement of the review team, largely physicochemical rather than statistical. In the non-obstetric horizontal adult, cerebrospinal fluid density is comparatively high, the glucose-free preparation behaves as a true isobaric solution, and the hyperbaric preparation therefore produces the higher block; the greater sympathectomy associated with that higher block accounts for the 30% versus 18% difference in mean arterial pressure decrease observed by Van Gessel. In the parturient at term, cerebrospinal fluid density falls to its lowest recorded value of approximately $1.00030 \text{ g}\cdot\text{mL}^{-1}$, with the consequence that the glucose-free preparation becomes relatively hypobaric and acquires a tendency to migrate cephalad; the block produced becomes not lower but higher and, critically, less predictable. It is this loss of predictability rather than any absolute difference in mean block height that is reflected in Vercauteren's observation that significantly more blocks in the plain group were either too high or too low for the intended surgery, and it provides the mechanistic bridge to the 21% versus 6% difference in hypotension and to the greater ephedrine consumption in that arm.^{24,7,11,21}

Loubert's three-arm trial furnishes the decisive experimental confirmation of this reasoning. By deliberately maintaining parturients in the sitting position for five minutes after injection, thereby simulating a difficult epidural catheter insertion, that investigator generated an ordered gradient in which the hypobaric solution produced the highest block (T6), the isobaric solution an intermediate block (T9) and the hyperbaric solution the lowest block (T10), with ephedrine requirements rising in exactly the same order by factors of 1.00, 1.83 and 3.00. This is a clean gravitational experiment: when the patient is upright the dense solution sediments to the sacral and lower lumbar segments and is haemodynamically the safest choice, whereas the least dense solution floats towards the mid-thoracic dermatomes and is the most demanding of vasopressor support. That the crude incidence of hypotension did not differ across these arms while vasopressor consumption differed threefold is itself instructive, and indicates that dichotomised hypotension is a

comparatively insensitive endpoint in an environment of protocolised prophylactic vasopressor administration.²⁰

Connolly's trial, which found that a tenfold difference in glucose concentration produced only minor differences in the resulting block at term, might appear to contradict this account, but in fact strengthens it: at term the density of the plain solution and the density of cerebrospinal fluid have converged so closely, and the confounding influences of engorged epidural veins, reduced cerebrospinal fluid volume and increased intra-abdominal pressure have become so prominent, that density ceases to be the dominant determinant of spread. The lesson for the obstetric anaesthetist is not that baricity is irrelevant but that its behaviour at term cannot be extrapolated from non-pregnant physiology.^{18,29}

Block quality: onset, spread and predictability

The predictability advantage of the hyperbaric formulation deserves particular emphasis because it is systematically under-reported. Standard trial reporting privileges the median or mean block height, which frequently does not differ between formulations; yet the parameter of clinical consequence is the proportion of blocks that fall outside the range adequate for the intended operation. Bannister's demonstration that dispersion narrowed from eleven to six dermatomes as glucose concentration rose is arguably the most clinically actionable single finding in this literature, and it is corroborated by Kokki's paediatric trial, in which the median maximum level was identical at T4 in both arms while the range extended from T1 to T12 in the isobaric arm against T1 to T7 in the hyperbaric arm, and by Vercauteren's finding of significantly more inadequate block heights in the plain group. Where the dose is deliberately low — as in modern low-dose caesarean protocols, in the frail elderly and in ambulatory surgery — the margin between an adequate and an inadequate block is narrow, and a formulation that halves the dispersion of the attained block height confers a clinically important advantage even when it does not shift the mean.^{16,8,7}

Onset data must be interpreted with explicit reference to patient position. The apparent contradiction between Bannister, who found the fastest onset with 8% glucose, and Frigon, who found significantly faster sensory and motor onset with the isobaric solution at five and ten minutes, dissolves entirely once it is recognised that the former injected into a horizontal patient and the

latter into a seated patient who remained seated. Frigon's associated finding that 28 of 39 epidural lidocaine top-ups were required by patients in the hyperbaric arm is the predictable consequence of sacral sedimentation, and constitutes a caution against the routine use of dense solutions where the patient must remain upright while an epidural catheter is sited.^{16,13}

Block duration and its operational consequences

The duration findings are the most consistent in this review and have the greatest logistical significance. A difference of 29 minutes in sensory block and 45 minutes in motor block is not a statistical curiosity: it determines whether a patient can be transferred from the post-anaesthesia care unit within the target interval, whether a same-day arthroplasty pathway is feasible, whether urinary catheterisation can be avoided, and how many cases can be scheduled in a given theatre session. Schwenk's trial makes this concrete, demonstrating that only 17.6% of patients receiving isobaric bupivacaine could ambulate at three to three and a half hours against 37.7% receiving the hyperbaric preparation, a risk ratio of 2.14 (95% CI 1.08 to 4.25). Conversely, in prolonged lower-limb surgery under a single-shot technique the longer block afforded by the isobaric solution is an unambiguous advantage, and Axelsson's quantitative dynamometry established that this prolongation is not merely a matter of subjective pinprick testing but reflects a genuinely prolonged depression of measurable muscle power.^{22,15}

A physiological explanation for the duration difference is available and is largely uncontroversial. The dextrose in a hyperbaric solution is rapidly diluted by cerebrospinal fluid, and the local anaesthetic, once its gravitational advantage has dissipated, is presented over a larger surface area of the spinal cord and cauda equina and is therefore cleared more rapidly by vascular absorption. A glucose-free solution deposited as a more compact bolus around the lumbar roots maintains a higher local concentration for longer, producing the more intense and more protracted lumbosacral block described consistently since the earliest reports.^{14,10,27}

Haemodynamic stability re-examined

The central clinical question — whether one formulation is safer for the cardiovascular system — receives a nuanced answer. Post-spinal hypotension is the arithmetic product of the extent of preganglionic sympathetic blockade and the compensatory capacity of the patient. Baricity

influences the first factor indirectly, through its effect on block height, and does not influence the second at all. Consequently, whenever a trial design equalises block height between arms, as occurs in the parturient in whom cerebrospinal fluid density has converged towards that of the plain solution, no haemodynamic difference emerges; and whenever a trial design permits block height to diverge, as in the horizontal non-obstetric patient, the haemodynamic difference follows the block height rather than the baricity. Van Gessel's finding of a 30% versus 18% fall in mean arterial pressure accompanied a difference in median sensory level of seven dermatomes; Carella's finding of an identical 33.1% fall in both arms accompanied a technique in which block height did not differ. Baricity is therefore best conceptualised not as an independent haemodynamic variable but as one of several determinants of block height, which is itself the proximate haemodynamic determinant.^{11,23,31}

Two further considerations attenuate the practical importance of formulation choice for haemodynamic stability. The first is dose. A retrospective analysis of 8,226 caesarean deliveries demonstrated that hypotension occurred at every dose of hyperbaric bupivacaine studied but was significantly more frequent at doses of 10 mg or more than below 10 mg (75.8% versus 62.9%; adjusted odds ratio 0.774, 95% CI 0.669 to 0.897), and randomised comparison of 9.5 mg with 6.5 mg produced hypotension rates of 68% and 16% respectively. The effect of halving the dose therefore dwarfs any effect attributable to the choice of formulation. The second is the vasopressor strategy. A network meta-analysis of 109 trials and 8,561 women established that metaraminol, norepinephrine and phenylephrine reduce the odds of hypotension by factors of approximately nine, eight and five-and-a-half respectively relative to control, effect sizes an order of magnitude greater than the 24% relative risk reduction observed for baricity in the present pooled analysis. In an environment in which prophylactic vasopressor infusion is standard, the residual signal attributable to baricity is small and may be clinically undetectable.^{30,32,33,34,35}

The discriminative perspective and its clinical meaning

The receiver-operating-characteristic analysis presented here formalises the foregoing argument. An area under the curve of 0.569, although statistically distinguishable from chance because its lower confidence limit of 0.521 exceeds 0.500, corresponds to negligible discrimination

by every conventional interpretive standard: a value below 0.60 is regarded as failing to provide clinically useful separation between those who will and those who will not experience the outcome. The Youden index at the empirical operating point is 0.129, and the crude absolute risk difference of 12.5 percentage points corresponds to a number needed to treat of eight. In other words, even if the point estimate favouring the hyperbaric formulation were accepted at face value, eight patients would have to receive the hyperbaric rather than the isobaric preparation for one episode of hypotension to be averted, and the identity of that one patient could not be predicted from the formulation in advance with anything approaching useful accuracy.

This finding should recalibrate a common clinical intuition. Anaesthetists who have observed a profound fall in arterial pressure after plain bupivacaine in a parturient, or after hyperbaric bupivacaine in an elderly patient positioned supine, understandably attribute causality to the formulation. The discrimination analysis indicates that such attributions are, in the great majority of instances, unwarranted: the formulation is a weak signal within a field dominated by dose, block height, baseline pressure, volume status, aortocaval compression and vasopressor policy. The appropriate response to a patient at high haemodynamic risk is therefore to reduce the dose, to secure a prophylactic vasopressor infusion and to control position and block height, not to change the ampoule.

Effect modification by position, injection level and technique

Three technical variables modify the baricity effect sufficiently to reverse its direction. Patient position is the most powerful, as demonstrated by the systematic reversal of the block-adequacy findings in every trial conducted in the sitting position. Injection level is the second: Sanderson showed that moving the injection from L3–4 to L2–3 produced a higher and more variable block irrespective of glucose concentration, an effect of magnitude comparable to that of glucose itself, because injection above the apex of the lumbar lordosis removes the anatomical barrier that otherwise arrests cephalad flow of a dense solution. Volume is the third and is, perhaps surprisingly, the least influential: Malinovsky demonstrated across six groups that volume had no significant influence on either cephalad spread or duration for either formulation, a finding that argues against the widespread practice of diluting local anaesthetic to increase spread. Injectate

temperature has more recently been shown to alter potency substantially, warming hyperbaric bupivacaine to body temperature reducing the median effective dose by approximately 16%, which represents another uncontrolled source of variability in the older literature.^{17,10,46}

Special populations

In children under approximately eight years of age, cardiovascular stability after subarachnoid block is preserved to a degree that has no adult counterpart, attributable to the relative immaturity of the sympathetic vascular tone and to the smaller proportion of circulating volume sequestered in the lower limbs. Both paediatric trials in this review recorded essentially no clinically important haemodynamic events across 100 infants and a further cohort of school-aged children, and the formulation question in paediatric practice reduces to one of block success alone, where the hyperbaric preparation demonstrated a significant advantage in infants (96% versus 82%). In the elderly, by contrast, the determinants of hypotension are age itself and the attained block height: Biboulet found that patients who became hypotensive were on average four years older than those who did not and had blocks approximately four dermatomes higher, and concluded that even 5 mg of bupivacaine is an excessive initial dose in this population. Titration through a spinal catheter reduces the fall in mean arterial pressure from approximately 40% to approximately 20% and reduces mean ephedrine consumption more than tenfold, an effect far exceeding anything attributable to baricity.^{8,9,12,44}

Comparison with previous systematic reviews and meta-analyses

Five previous syntheses bear directly on this question and, in accordance with the prespecified protocol, were excluded from the characteristics tables and the quantitative synthesis while being retained here for interpretative comparison. The Cochrane review of elective caesarean section, in its 2013 version, included six trials and 394 participants and reported that conversion to general anaesthesia was less likely with hyperbaric bupivacaine (RR 0.17, 95% CI 0.03 to 0.94) and that the time to a T4 level was shorter by 1.06 minutes. Its 2016 update incorporated three additional trials, giving ten studies and 614 participants, and the effect on conversion to general anaesthesia was no longer statistically significant (RR 0.33, 95% CI 0.09 to 1.17), although the time-to-T4 advantage persisted (MD -1.06 min, 95% CI -1.80 to -0.31, moderate-quality

evidence). No difference was found in supplemental analgesia (RR 0.61, 95% CI 0.26 to 1.41), ephedrine requirement (RR 0.89, 95% CI 0.57 to 1.38), nausea and vomiting (RR 0.99, 95% CI 0.57 to 1.72), headache (OR 1.82, 95% CI 0.47 to 6.99) or high block (RR 0.88, 95% CI 0.16 to 4.90). The corresponding meta-analysis of adult non-caesarean surgery included 16 trials and 724 participants and found no difference in conversion to general anaesthesia (RR 0.60, 95% CI 0.08 to 4.41), hypotension (RR 1.15, 95% CI 0.69 to 1.92) or nausea and vomiting (RR 0.29, 95% CI 0.06 to 1.32), but did find significantly faster motor onset with hyperbaric bupivacaine and significantly longer sensory and motor block with isobaric bupivacaine.^{1,2,3,4,5}

The present review is consistent with all of these syntheses in its estimates of block timing and duration, and diverges from them in three respects. First, by analysing obstetric and non-obstetric evidence within a common framework, it identifies population-specific cerebrospinal fluid density as the probable explanation for the fact that the earlier syntheses reached apparently discordant conclusions on hypotension. Second, by extracting event data from a large prospective obstetric cohort published after the most recent Cochrane update, it demonstrates that a significant reduction in both hypotension and vasopressor requirement is detectable with hyperbaric bupivacaine in a contemporary, high-volume, low-resource obstetric setting, while showing that this signal is attenuated to non-significance when pooled with non-obstetric data. Third, and uniquely, it quantifies the discriminative rather than merely the average effect and thereby places an upper bound on the explanatory contribution of formulation choice, an analysis that no previous synthesis has performed.²¹

Comparison with alternative agents and adjunctive strategies

The baricity question should be placed in the context of the wider pharmacological alternatives. Hyperbaric ropivacaine provides reliable anaesthesia of shorter duration than bupivacaine with earlier mobilisation and micturition and significantly less requirement for treatment of hypotension, and the addition of glucose to ropivacaine increases the speed of onset, the reliability of the block, the duration of useful block for perineal surgery and the speed of recovery, plain ropivacaine being unreliable above L1. Hyperbaric levobupivacaine is clinically indistinguishable from racemic bupivacaine across doses of 4 to 12 mg. Hyperbaric prilocaine

produces a shorter and more reliable motor block than heavy bupivacaine for caesarean section without differences in maternal hypotension, Apgar score or umbilical pH. Mepivacaine permits earlier ambulation and same-day discharge than either bupivacaine formulation after hip arthroplasty. These comparisons indicate that where the clinical objective is a short, reliable, rapidly regressing block, the choice of a different molecule is likely to be more effective than a change in the baricity of bupivacaine; and where the objective is haemodynamic stability, dose reduction and vasopressor prophylaxis are likely to be more effective than either.^{36,37,38,39,43,22}

A proposed clinical decision framework

Synthesising the foregoing, the review team proposes that formulation choice be determined by four sequential questions rather than by institutional habit: what block height is required; what block duration is required; in what position will the patient be at and immediately after injection; and how tolerant is this particular patient of sympathectomy. The resulting recommendations are set out in Table 22.

Table 22. Proposed evidence-based framework for the selection of bupivacaine formulation

Clinical scenario	Preferred formulation	Supporting evidence	Practical qualification
Elective caesarean delivery, supine with lateral tilt	Hyperbaric	Faster attainment of T4; lower rate of inadequate block height; lower hypotension and vasopressor requirement in the largest prospective cohort	Combine with a low dose and a prophylactic vasopressor infusion; the formulation is a secondary consideration.
Caesarean delivery in which the patient must remain seated (difficult epidural catheter insertion)	Hyperbaric	Lowest block height and lowest ephedrine requirement of the three baricity strata under a five-minute seated protocol	Anticipate a lower block; verify the level before incision.

Prolonged lower-limb or lower-abdominal surgery under single-shot spinal	Isobaric	Sensory block approximately 29 minutes and motor block approximately 45 minutes longer	Accept a lower and less predictable block height; consider a catheter technique if the duration is critical.
Ambulatory or day-case surgery requiring rapid recovery	Hyperbaric	Earlier return of motor function and a twofold higher rate of ambulation at three to three and a half hours	Consider mepivacaine or hyperbaric prilocaine if same-day discharge is the dominant objective.
Perineal, anorectal or saddle block	Hyperbaric	Reliable sacral concentration of a dense solution in the sitting position	Maintain the sitting position for the interval specified by local protocol.
Unilateral lower-limb block in the lateral position	Hyperbaric with the operative side dependent	Unilateral block preserved in 68% after repositioning versus 24% with the hypobaric comparator	Maintain the lateral position for at least 15 minutes after injection.
Elderly patient with limited cardiovascular reserve, supine	Either formulation, at a reduced and titrated dose	Age and block height rather than baricity determine hypotension; catheter titration halves the fall in mean arterial pressure	Prioritise dose reduction and incremental titration over formulation choice.
Paediatric spinal anaesthesia in infants	Hyperbaric	Block success 96% versus 82% ($p = 0.025$)	Haemodynamic events are rare in this age group irrespective of formulation.

Total knee or hip arthroplasty in the horizontal patient	Either, according to the required duration	No difference in maximal fall in mean arterial pressure or nadir mean arterial pressure	Where early ambulation is the objective, the shorter block of the hyperbaric preparation is advantageous.
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Implications for practice in resource-limited settings

In settings where continuous invasive monitoring and prophylactic vasopressor infusions are not routinely available, the incidence of post-spinal hypotension at caesarean delivery is high: a cross-sectional study of 410 women in the same institution from which the largest cohort in this review derives reported an incidence of 64%, with sensory block height above T6, low baseline systolic pressure, neonatal weight of 4 kg or more and operator inexperience emerging as independent predictors. In that environment a formulation that halves the dispersion of block height and reduces the vasopressor requirement by 61% is of greater relative value than in a setting where a norepinephrine infusion is commenced before the block is sited. The review team therefore regards the hyperbaric formulation as the pragmatic default for obstetric spinal anaesthesia in resource-limited practice, while emphasising that the dominant modifiable determinants remain dose selection, attention to left uterine displacement and the availability of an effective vasopressor.^{31,21,33}

Strengths of this review

The review has several methodological strengths. The protocol was prespecified and the outcome hierarchy was fixed before data extraction. Fourteen outcome domains were examined, each supported by an outcome-specific evidence table, which is a broader coverage than any previous synthesis of this question. Systematic reviews and meta-analyses were rigorously excluded from the characteristics tables and from all quantitative synthesis, eliminating the double-counting of primary data that has affected some previous narrative treatments, while being retained transparently as interpretative comparators. Every reference was individually verified through an academic search engine and is accompanied by both a digital object identifier and a permanent record link. Both randomised and observational evidence was appraised with design-appropriate

instruments. Finally, the discrimination analysis introduces a quantitative framework for distinguishing between a statistically detectable difference in incidence and a clinically useful predictive relationship, a distinction that is frequently elided in the interpretation of comparative anaesthetic trials.

Recommendations for future research

Four research priorities emerge. The first is an adequately powered, registered, multicentre randomised trial in the obstetric population comparing hyperbaric with isobaric bupivacaine at a fixed low dose under a standardised prophylactic norepinephrine infusion, with the incidence of hypotension defined by a single prespecified threshold and with the attained sensory block height recorded as a mediator; a trial detecting a reduction from 60% to 45% with 90% power at the 5% significance level would require approximately 460 participants. The second is an individual-participant-data meta-analysis of the existing trials, which would permit formal mediation analysis of the pathway from baricity through block height to hypotension and would resolve the discrimination question definitively. The third is the routine reporting of the dispersion of attained block height, and not merely its central tendency, as a primary endpoint in all future spinal anaesthesia trials, since predictability rather than average height is the parameter of clinical consequence. The fourth is the systematic measurement of cerebrospinal fluid density in trial participants, which is technically straightforward with modern oscillating-tube densitometry and would allow baricity to be analysed as the continuous variable it actually is rather than as the dichotomy it is conventionally assumed to be.^{24,26,33}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review of 20 primary comparative studies enrolling 1,281 participants demonstrates that the baricity of intrathecal bupivacaine is a genuine and physically deterministic modifier of neuraxial block characteristics, but a weak and inconsistent modifier of clinically important haemodynamic outcomes. Hyperbaric bupivacaine produces a faster onset of motor blockade (pooled mean difference -4.6 minutes, 95% CI -7.5 to -1.7; $p = 0.002$), a shorter interval to a T4 sensory level in obstetric practice (mean difference -1.06 minutes, 95% CI -1.80 to

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-0.31; $p = 0.005$), a higher and markedly more predictable block height in the horizontal patient, and a significantly lower rate of block failure in the paediatric setting (RR 0.22, 95% CI 0.05 to 0.98). Isobaric bupivacaine produces a significantly longer sensory block (mean difference 29.4 minutes, 95% CI 15.5 to 43.3; $p < 0.001$) and motor block (45.2 minutes, 95% CI 24.2 to 66.3; $p < 0.001$), at the cost of a slower, lower and considerably less predictable block.

With respect to haemodynamic stability, the evidence supports a conditional rather than an absolute conclusion. In contemporary obstetric practice the hyperbaric formulation was associated with significantly less hypotension (60% versus 82%; RR 0.73, 95% CI 0.56 to 0.95) and significantly less vasopressor requirement (14% versus 36%; RR 0.39, 95% CI 0.18 to 0.85) in the largest prospective cohort, and with a significant ordered reduction in ephedrine consumption across baricity strata in a randomised three-arm trial. When obstetric and non-obstetric data are pooled, however, the effect on hypotension is not statistically significant (RR 0.76, 95% CI 0.47 to 1.22; $I^2 = 49.7\%$), and the most rigorous contemporary trial in arthroplasty found the maximal fall in mean arterial pressure to be identical between formulations. The exploratory discrimination analysis places this in proportion: the area under the receiver-operating-characteristic curve for baricity with respect to post-spinal hypotension was 0.569 (95% CI 0.521 to 0.642), formally better than chance but of negligible clinical utility.

The overall conclusion is therefore that neither formulation is universally superior. Hyperbaric bupivacaine should be regarded as the formulation of choice where block predictability, rapid attainment of a defined thoracic level or rapid recovery is the governing requirement, most notably in obstetric anaesthesia, in ambulatory surgery and in paediatric practice. Isobaric bupivacaine should be preferred where a prolonged block is required and a lower block height is acceptable. Formulation choice should be made on the basis of the required block level, the required duration, the patient's position at and after injection and the population-specific relationship between injectate density and cerebrospinal fluid density, and should not be relied upon as a primary strategy for the prevention of post-spinal hypotension, for which dose reduction, positional management and prophylactic vasopressor administration remain substantially more effective.

Recommendations for clinical practice

- (1) Select the bupivacaine formulation according to the required block height and duration rather than according to institutional habit, using the framework set out in Table 23.
- (2) In elective caesarean delivery, prefer hyperbaric bupivacaine for its faster attainment of a T4 level and its lower proportion of inadequate block heights, and combine it with a low dose and a prophylactic vasopressor infusion.
- (3) Do not rely on a change of formulation as a strategy for preventing post-spinal hypotension; reduce the dose, maintain left uterine displacement or an equivalent positional manoeuvre, and commence a prophylactic vasopressor.
- (4) Where the patient must remain seated after injection, recognise that a dense solution will sediment caudally and anticipate a lower block, and where the patient is placed supine immediately, anticipate a mid-thoracic block with the same solution.
- (5) In prolonged lower-limb surgery under a single-shot technique, prefer isobaric bupivacaine for its additional 29 minutes of sensory and 45 minutes of motor block, or use a catheter technique if duration is critical.
- (6) In ambulatory and enhanced-recovery arthroplasty pathways, prefer hyperbaric bupivacaine for its earlier return of motor function, and consider mepivacaine or hyperbaric prilocaine where same-day discharge is the dominant objective.
- (7) In infants and young children requiring spinal anaesthesia, prefer hyperbaric bupivacaine on the grounds of a significantly higher block success rate.
- (8) In patients aged 75 years and over, prioritise dose reduction and incremental titration, ideally through a spinal catheter, over the choice of formulation.
- (9) Verify the attained sensory level before surgical incision in every case, irrespective of formulation, since block height and not baricity is the proximate determinant of both surgical adequacy and cardiovascular effect.
- (10) Document the attained maximum sensory level routinely, so that departmental audit can relate haemodynamic events to block height rather than to formulation.

Recommendations for research and education

- (1) Conduct an adequately powered, registered, multicentre randomised trial in the obstetric population, comparing formulations at a fixed low dose under a standardised prophylactic norepinephrine infusion, with a single prespecified definition of hypotension and with attained block height recorded as a mediator; approximately 460 participants would be required to detect a reduction from 60% to 45% with 90% power.
- (2) Undertake an individual-participant-data meta-analysis of the existing randomised trials to permit formal mediation analysis of the pathway from baricity through block height to hypotension, and to derive a properly specified discrimination estimate.
- (3) Report the dispersion of the attained block height, and not only its central tendency, as a primary endpoint in all future trials of subarachnoid anaesthesia.
- (4) Measure cerebrospinal fluid density in trial participants using oscillating-tube densitometry, so that baricity can be analysed as a continuous rather than a dichotomous exposure.
- (5) Incorporate validated patient-centred outcomes, including quality-of-recovery instruments and satisfaction measures, and report the economic consequences of the difference in block duration.
- (6) Include the physicochemical basis of intrathecal drug distribution, and specifically the population-specific variation in cerebrospinal fluid density, in the core curriculum of specialist training in anaesthesiology.

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Data availability. All data analysed in this review are contained within the published reports cited in the reference list, each of which is accompanied by a digital object identifier and a permanent academic record link. The extraction spreadsheet and the analytical scripts used for the pooled

estimates and the discrimination analysis are available from the corresponding author on reasonable request.

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