BMJ Open Intrathecal hyperbaric versus isobaric bupivacaine for adult non-caesarean-section surgery: systematic review protocol

Vishal Uppal,¹ Harsha Shanthanna,² Christopher Prabhakar,³ Dolores M McKeen¹

To cite: Uppal V, Shanthanna H, Prabhakar C, *et al.* Intrathecal hyperbaric versus isobaric bupivacaine for adult non-caesarean-section surgery: systematic review protocol. *BMJ Open* 2016;**6**:e010885. doi:10.1136/bmjopen-2015-010885

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2015-010885>).

Received 16 December 2015
Revised 21 March 2016
Accepted 19 April 2016

CrossMark

¹Dalhousie Department of Anesthesia, Perioperative Medicine and Pain Management, Nova Scotia Health Authority and IWK Health Centre, Halifax, Nova Scotia, Canada

²Department of Anesthesia, McMaster University, St Joseph's Health Care, Hamilton, Ontario, Canada

³Department of Anesthesia, University of British Columbia, St. Paul's Hospital, Vancouver, British Columbia, Canada

Correspondence to

Dr Vishal Uppal;
v.uppal@dal.ca

ABSTRACT

Introduction: Bupivacaine is the most commonly used local anaesthetic for spinal anaesthesia (SA). There are two forms of commercially available bupivacaine; isobaric bupivacaine (IB): a formulation with a specific gravity or density equal to cerebrospinal fluid, and hyperbaric bupivacaine (HB): a formulation with density heavier than cerebrospinal fluid. The difference in densities of the two available preparations is believed to affect the diffusion pattern that determines the effectiveness, spread and side-effect profile of bupivacaine. This systematic review will summarise the best available evidence regarding the effectiveness and safety on the use of HB compared with IB, when used to provide SA for surgery. Primarily, we will analyse the need for conversion to general anaesthesia. As secondary outcomes, we will compare the incidence of hypotension, incidence of nausea/vomiting, the onset time and duration of anaesthesia.

Methods and analysis: We will search key electronic databases using search strategy (1) injections, spinal OR intrathecal OR subarachnoid; (2) bupivacaine OR levobupivacaine; (3) hypobaric OR isobaric OR plain; (4) baricity. We will search MEDLINE, EMBASE and Cochrane databases, from their inception for randomised controlled trials, with no restrictions on language. Caesarean section surgery will be excluded. 2 reviewers will independently extract the data using a standardised form. Extracted items will include study characteristics, risk of bias domains, as per modified Cochrane risk of bias, participant disposition and study outcomes. We will conduct a meta-analysis for variables that can be compared across the studies. We will evaluate clinical heterogeneity by qualitatively appraising differences in study characteristics in participants, interventions and the outcomes assessed. We will report our findings as relative risks (dichotomous), and weighted mean differences (continuous) for individual outcomes, along with their 95% CIs.

Ethics and dissemination: We plan to submit, and will publish, our findings in a peer-reviewed scientific journal, and present our results at national and international meetings.

Trial registration number: CRD42015017672.

INTRODUCTION

More than 100 million surgical procedures are performed in the USA and Canada each year.¹ Approximately, 5%, or 5 million surgical procedures, are performed under spinal anaesthesia (SA).² SA allows for an effective intraoperative anaesthesia with good surgical conditions for surgeries on the lower abdomen, pelvis and lower extremity areas. SA is performed by injecting a local anaesthetic (LA) into the cerebrospinal fluid (CSF) in the subarachnoid space. This produces a rapid-onset, intense, sensory and motor blockade, as well as sympathetic blockade.³ Opioids, such as fentanyl, sufentanil and morphine are sometimes coadministered to supplement the effect (block duration or block quality) of the LA. Such studies will not be considered within the scope of this review.

Bupivacaine hydrochloride (HCL) is an aminoacyl LA, and is the most commonly used LA medication for SA. There are two forms of commercially available bupivacaine; isobaric bupivacaine (IB): a formulation with density equal to that of CSF and hyperbaric bupivacaine (HB): a formulation with density heavier than CSF. HB is made dense by the addition of glucose (80 mg/mL) to isobaric or plain bupivacaine. The difference in densities of the two available preparations is believed to affect their diffusion patterns and distribution after injection into the CSF in the subarachnoid space. The diffusion pattern determines the effectiveness, spread (dermatome height or block height) and side-effect profile of bupivacaine.⁴

Several trials have shown that HB appears to cause more predictable sensory blockade than IB.⁵ On the other hand, IB has been found to produce a longer duration of SA.^{6 7} The choice between IB and HB is usually made in consideration with the surgical

factors. There is a large regional and institutional variation in the practice patterns or clinical usage of IB versus HB.⁸ The successful conduct of surgery under SA requires effective and complete blockade of the surgical segments, which may be affected by the choice of bupivacaine. More importantly, for the patients, the choice between HB and IB may determine the failure rate, which would determine whether a conversion to general anaesthesia (GA) or cancellation of surgery is required.

Trials, which have so far compared IB with HB, have not provided consistent results. Vernhiet *et al*⁹ suggested that use of HB for SA is associated with lower failure rate compared to IB, however, there was lower incidence of hypotension with IB. Some studies have reported that the incidence of hypotension is higher with use of HB for SA.^{10–14} On the contrary, others have reported similar incidences of hypotension,^{15–18} or a lower incidence of hypotension with use of HB compared to IB.¹⁹ The incidence of side effects such as hypotension, bradycardia, nausea and vomiting may be altered by the LA spread (or number) of nerve roots/segments blocked in the spinal cord, and hence, may differ between IB and HB. HB for SA has been found particularly useful for patients undergoing unilateral surgical operations, as a unilateral block may be possible with a more favourable side-effect profile.^{20–22}

Similarly, there is conflicting evidence related to time of onset of block, maximum dermatomal spread, time to block regression, and the duration of motor block. In general, most studies suggest that the HB produces more extensive dermatomal spread, shorter duration of sensory and motor block,¹⁰ however, others disagree.^{7, 23–24} Longer duration of motor and sensory block produced by IB has been proposed to be useful for longer surgical procedures.^{25–26}

This systematic review will summarise the best available evidence regarding the effectiveness and safety on the use of HB compared to IB, when used to provide SA for surgery. We are unaware of any previously published systematic review addressing this question. The results of this review will enable clinicians to make an evidence-based choice on type of bupivacaine preparation they should use while performing SA for non-caesarean-section surgery.

Objectives

Primary objective

1. To determine the effectiveness of HB compared to IB for SA in patients undergoing surgeries of the lower body; assessed as success rate of SA.

Secondary objectives

1. To determine the safety of HB compared to IB for SA in patients undergoing surgeries of the lower body; assessed as use of medications for hypotension, nausea-vomiting (NV) and bradycardia.
2. To determine the onset time, duration of blockade and regression of spinal block, compared between

HB and IB for SA in patients undergoing surgeries of the lower body.

METHODS

Our review protocol has been registered with PROSPERO (registration number PROSPERO 2015: CRD42015017672). This protocol has been prepared for publication according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.²⁷

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials (RCTs), published in any language.

Types of participants

We will include adult patients (aged >18 years) undergoing SA for elective surgical procedures on the lower abdomen, pelvis, or the lower extremities. We will exclude patients undergoing emergency surgery or caesarean section.

Types of interventions

Included studies must have compared HB versus IB introduced as a single-shot SA. We will include only the studies that have used standard HB (ie, bupivacaine with glucose 80 mg/mL. Studies using additives in the form of opioids, or a mixture of LAs will be excluded. The studies that have compared different dosages (mg) of LA will be excluded. We will also exclude studies, which included the elective use of GA, or any other modality of regional analgesia (nerve block or epidural) techniques. Finally, studies that used epidural volume expansion will also be excluded.

Types of outcome measures

Primary outcomes

1. Failure rate of SA, assessed as either the need for conversion to GA, or as cancellation of surgery.

Secondary outcomes

1. Incidence of intraoperative hypotension: defined as the need for use of vasopressors.
2. Incidence of intraoperative NV: defined as number of patients needing treatment. The units of measurement will be considered as one patient, and not episodes of NV.
3. Onset time: defined as the time from the performance of SA to the time when patients were deemed suitable for the start of surgery.
4. Time to regression of sensory and motor block, as defined by the authors in each publication.

Search methods for identification of studies

Electronic searches

The following databases will be searched: MEDLINE, EMBASE and the Cochrane Central Register of

Controlled Trials (CENTRAL). In addition, we will conduct searches of trial registries for completion of search and cross-check with our search results. Further, we will contact investigators for study reports of any completed studies which have not been published.

Search strategy is provided in online supplementary appendix 1.

Selection of studies for inclusion in the review

Study selection will be performed in two stages with two independent reviewers (VU and CP). At the first stage, title and abstracts will be screened, followed by full-text screening. Selection criteria will include: RCT; adults (>18 years) having SA for non-caesarean-section surgeries; bupivacaine or levobupivacaine used as hyperbaric versus isobaric in at least two of the study groups. The Proforma for screening is attached as online supplementary appendix 2. Any discrepancy will be settled by mutual agreement or by an arbitrator (DM). We will calculate κ scoring for agreement on full-text study selection.

Data extraction

Two reviewers will independently extract the data using a standardised form. Extracted items will include study characteristics, risk of bias (RoB) domains—as per modified Cochrane RoB, participant disposition, and study outcomes. The data will be captured using electronic forms.

Assessment of RoB in included studies

We will assess the RoB using a modified Cochrane RoB tool.²⁸ Only the following six domains will be considered. The considered domains will include the following:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting.

Each domain will be graded as low risk, high risk, or unclear RoB.

Outcomes and prioritisation

We will prioritise the intention-to-treat approach, and consider complete case analysis for primary analysis. We will include only the studies that have used standard HB (ie, bupivacaine with glucose 80 mg/mL. If there is more than a single group of HB, the group with 8% dextrose will be compared with the IB group. Studies reporting the success rate of SA will be considered for primary analysis as a dichotomous outcome measure of success or failure. Studies reporting the use of medications for side effects will also be assessed using a dichotomous outcome measure of yes or no. For continuous outcome measurements of onset time and duration of block, we will convert the reported time into minutes for

purposes of analysis and reporting. Block time regression will be considered as rate of regression (spinal levels) in a unit time (minutes), for analysis and reporting. Pooling of outcomes will be done whenever there are three or more studies for a particular outcome.

Data synthesis and analysis of outcomes

Analysis and synthesis will be carried out using Review Manager (RevMan) (computer programme). V.5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; and Microsoft Excel programme. Pooling will be done using a fixed-effects model. However, if the I^2 for a pooled outcome is >25% indicative of significant inconsistency, we will analyse and report using a random-effects model. Dichotomous outcomes will be reported as relative risks (RR), and continuous outcomes weighted mean differences (WMD) for time of onset, duration and rate of regression. Outcomes will be reported with their effect estimates along with 95% CI.

Assessment of heterogeneity

We will evaluate clinical heterogeneity by qualitatively appraising differences in study characteristics in participants, interventions, the outcomes assessed and study methodologies. We will also evaluate and investigate the degree of statistical heterogeneity by visual inspection of forest plots and, more formally, by the I^2 statistic.²⁹ Measure of heterogeneity will be reported as χ^2 , with a threshold of p set at 0.10, and inconsistency across studies as a proportion of I^2 .

Addressing potential biases

Publication bias will be assessed using a funnel plot if there are more than 10 studies included in a meta-analysis. Selective outcome reporting is difficult to identify when the study protocols are not available, or published. For our review, we will consider the possibility of selective outcome reporting if the studies have one or more of the characteristics identified within the Cochrane RoB tool. (http://handbook.cochrane.org/chapter_8/table_8_5_d_criteria_for_judging_risk_of_bias_in_the_risk_of.htm).

We do not expect any loss to follow-up (LTFU) for the primary outcome as it involves a follow-up of less than a single day during the hospital stay. Any identified high-risk bias in the components of selection, performance and detection will be noted across the studies, and we will conduct a subgroup analysis on a RoB component-by-component basis, only if there is considerable variability within the RoB component.

Subgroup and sensitivity analysis

Subgroup analysis

We will conduct a subgroup analysis for studies with lateral/unilateral block, versus supine positioning, post-SA. Surgeries needing unilateral SA, such as for amputation or lower limb surgeries, may involve

differences in drug volume and positional variation in the actions of SA. Hence, they will be considered separately under a different subgroup compared to patients with supine position after spinal injection. This will be performed only on the primary outcome.

Sensitivity analysis

We plan the following sensitivity analyses:

1. Exclusion of studies judged as having a high or unclear RoB. We will conduct this subgroup analysis on a RoB component-by-component basis, only if there is considerable variability within the RoB component. This will be done only on the primary outcome.
2. Studies using levobupivacaine compared to bupivacaine: although there is no clear literature on the clinical differences in the effects of these two isomers of bupivacaine, we think it is possible that the effects may be different.³⁰ We will conduct a sensitivity analysis on the primary outcome to explore this difference.
3. Studies using prophylactic vasopressors: we believe that the chances of hypotension, bradycardia and NV could be affected by the use of either of the above interventions, hence, we will perform a sensitivity analysis to explore the difference in the outcomes of hypotension, bradycardia and NV, by exclusion of studies using either of the above interventions.
4. Studies reporting more than 10% of spinal injections as repeat injections.

Addressing heterogeneity

Statistical heterogeneity will be calculated using Cochrane's Q test, with a threshold of p value set at 0.10, and I² statistic to describe the percentage variability in individual effect estimates that could be due to true differences between the studies rather than a sampling error. To explore potential sources of heterogeneity, we will conduct the subgroup analysis based on patient positioning soon after SA, and also conduct sensitivity analysis based on studies with high RoB, studies using prophylactic vasopressors, studies using levobupivacaine, and studies with >10% of injections as repeat injections.

Interpretation and reporting

We will report our findings as RRs (dichotomous) and WMDs (continuous) for individual outcomes, along with their 95% CIs. We will also report the findings in measures of RR reduction and absolute risk reduction. Rating of quality of evidence, confidence in effect estimates will be reported using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. This will enable us to report our study findings in the form of 'summary of findings' table, and allow us to evaluate the certainty in effect estimates.

DISCUSSION

The choice between IB and HB is one among the many technical factors that determine the clinical effects of SA.⁴ However, it has been shown that factors such as barbotage, rate of injection and the level of injection, may not make much difference in controlled studies. Although there may be observable differences in the spread and temporal effects of spinal blockade, we think these effects may not be significantly different when considered in the domains of patient-important outcomes such as success or failure, and safety in the form of NV or cardiac effects. We believe that this comprehensive systematic review will enable us to answer this question, and will benefit by helping in decision-making based on existing evidence. We plan to report our trial results in an appropriate journal of good scientific impact. Results will be presented at local, national and international meetings (the Departmental Research Day, the Canadian Anesthesia Society (CAS) meeting 2017, and International Anesthesia Research Society (IARS) meeting 2017), and anticipate high-impact journal publication. Results disseminated on social media such as Twitter (@ropivacaine, @dolores.mckeen) and tracked by Altametrics.

Twitter Follow Christopher Prabhakar at @ChrisPrabhakar

Acknowledgements The authors would like to thank Ms Darlene Chapman (Manager, Library Services) and Ms Pamela Parker (Library Assistant) from IWK Health Centre (Halifax) for helping us with literature search. We would like to thank Department of Anesthesia, Dalhousie University for supporting open access publication of this protocol.

Contributors VU and CP contributed to the conception of the study. All authors contributed to the study design. VU and HS drafted the manuscript protocol. VU, CP and DMM will undertake screening of studies. All authors approve the publication of the protocol.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

1. Gan TJ, Habib AS, Miller TE, *et al.* Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin* 2014;30:149–60.
2. Cook TM, Counsell D, Wildsmith JA, *et al.* Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009;102:179–90.
3. Miller RD. *Miller's anesthesia*. 8th edn. Philadelphia, PA: Elsevier/Saunders, 2015.
4. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985;64:715–30.
5. Sia AT, Tan KH, Sng BL, *et al.* Use of hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev* 2013;5:CD005143.
6. Helmi M. Isobaric bupivacaine has rapid onset and longer duration compared to hyperbaric bupivacaine for subarachnoid block. *Reg Anesth Pain Med* 2010;35:E44.
7. Martin R, Frigon C, Chrétien A, *et al.* Onset of spinal block is more rapid with isobaric than hyperbaric bupivacaine. *Can J Anaesth* 2000;47:43–6.

8. Aiono-Le Tagaloa L, Butwick AJ, Carvalho B. A survey of perioperative and postoperative anesthetic practices for cesarean delivery. *Anesthesiol Res Pract* 2009;2009:510642.
9. Vernhiet J, Cheruy D, Maindivide J, *et al.* Spinal anesthesia with bupivacaine. Comparative study of 2 hyperbaric and isobaric solutions. *Ann Fr Anesth Reanim* 1984;3:252–5.
10. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *Br J Anaesth* 1981; 53:279–82.
11. Critchley LA, Morley AP, Derrick J. The influence of baricity on the haemodynamic effects of intrathecal bupivacaine 0.5%. *Anaesthesia* 1999;54:469–74.
12. Cui Y. Comparison of lunbar anesthesia with hyperbaric and isobaric bupivacaine at various concentrations for transurethral electrovaporization of the prostate. *Chin J New Drugs* 2008;17:1254–6.
13. Phelan DM, MacEvilly M. A comparison of hyper- and isobaric solutions of bupivacaine for subarachnoid block. *Anaesth Intensive Care* 1984;12:101–7.
14. Solakovic N. Comparison of hemodynamic effects of hyperbaric and isobaric bupivacaine in spinal anesthesia. *Med Arh* 2010;64:11–14.
15. Kathuria S, Kaul TK, Gautam PL, *et al.* Bupivacaine: isobaric vs. hyperbaric in spinal anaesthesia. *J Anaesthesiol Clin Pharmacol* 1998;14:211–15.
16. Muralidhar V, Kaul HL. Comparative evaluation of spinal anaesthesia with four different bupivacaine (0.5%) solutions with varying glucose concentrations. *J Anaesthesiol Clin Pharmacol* 1999;15:165–8.
17. Siaens A, De Rood M. Effects of baricity and mass of bupivacaine solutions in spinal anesthesia. *Acta Anaesthesiol Belg* 1987;38:89–95.
18. Suzuki H, Ogawa S, Hanaoka K, *et al.* Clinical study of AJ-007 (bupivacaine) in spinal anesthesia—investigation of clinical dosage of isobaric and hyperbaric formulations. *Masui* 1998;47:447–65.
19. Okazaki S, Ogata K, Kawaguchi E, *et al.* Subarachnoid anesthesia with hyperbaric bupivacaine. *Masui* 1989;38:923–6.
20. Kaya M, Oğuz S, Aslan K, *et al.* A low-dose bupivacaine: a comparison of hyperbaric and hypobaric solutions for unilateral spinal anesthesia. *Reg Anesth Pain Med* 2004;29:17–22.
21. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT. A low dose of plain or hyperbaric bupivacaine for unilateral spinal anesthesia. *Reg Anesth Pain Med* 2000;25:605–10.
22. Stefanov C, Tilkijan M, Kadijska M, *et al.* Unilateral spinal anesthesia for arthroscopic operations of the knee—Clinical and pharmaco-economical effects of the use of hyperbaric bupivacaine. *Anaesthesiol Intensive Care* 2005;32:31–6.
23. Krüger D, Iphie P, Nolte H, *et al.* Effect of glucose concentration on spinal anesthesia with bupivacaine 0.5%. *Reg Anaesth* 1983;6:1–3.
24. Malinovsky J-M, Renaud G, Le Corre P, *et al.* Intrathecal bupivacaine in humans: influence of volume and baricity of solutions. *Anesthesiology* 1999;91:1260–6.
25. Badalov P, Celebi H, Montes B. Comparison of spinal anesthesia with isobaric 0.5 BUPIVACAINE IN THE PRONE OR JACKKNIFE POSITION WITH HYPERBARIC 0.5 bupivacaine in the sitting position for anorectal surgery. *Gazi Med J* 2005;16:176–9.
26. Alston RP. Spinal anaesthesia with 0.5% bupivacaine 3 ml: comparison of plain and hyperbaric solutions administered to seated patients. *Br J Anaesth* 1988;61:385–9.
27. Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
28. Higgins JPT, Altman DG, Gotzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
29. Higgins J, Thompson S, Deeks J, *et al.* Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002;7:51–61.
30. Hakan Erbay R, Ermumcu O, Hanci V, *et al.* A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: a randomized controlled trial. *Minerva Anesthesiol* 2010;76:992–1001.