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INTRATHECAL HYPERBARIC VERSUS ISOBARIC BUPIVACAINE FOR ADULT NON- CAESAREAN SECTION SURGERY: SYSTEMATIC REVIEW PROTOCOL

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Key words: Spinal anesthesia, Hyperbaric Bupivacaine, Isobaric Bupivacaine,

Levobupivacinaine, non-caesarean-section surgery

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ABSTRACT

Introduction: Bupivacaine is the most commonly used local anesthetic for spinal anesthesia. 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 (CSF). The difference in densities of the two available preparations is believed to affect the distribution of this medication after injection into the subarachnoid space. The diffusion pattern determines the effectiveness, spread and side effect profile of bupivacaine. This systematic review will summarize the best available evidence regarding the effectiveness and safety on the use of HB compared to IB, when used to provide spinal anesthesia for surgery.

Methods and analysis: We will search key electronic database using search strategy (1) Injections, Spinal (2) bupivacaine OR levobupivacaine (3) Hypobaric OR isobaric OR plain (4) Baricity. We will search for randomized controlled clinical trials (RCTs), published in any language between 1980 and 2015. We will exclude patients undergoing emergency surgery or caesarean section. Two reviewers will independently extract the data using a standardized 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% confidence intervals.

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. Dissemination will be both in electronic and paper format.

Trial registration number: PROSPERO 2015:CRD42015017672

INTRODUCTION

More than 100 million surgical procedures are performed in USA and Canada each year.[1] Approximately, 5% or 5 million of surgical procedures are performed under spinal anesthesia (SA).[2] SA allows for an effective intraoperative anesthesia with good surgical conditions for surgeries on lower abdomen, pelvis and lower extremity. SA is performed by injecting a local anesthetic (LA) into the cerebrospinal fluid (CSF) in the subarachnoid space. Opioids, such as fentanyl, sufentanil, and morphine are sometimes co-administered to supplement the effect (block duration or block quality) of the LA.

Bupivacaine hydrochloride (HCL) is an aminoacyl local anesthetic 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 cerebrospinal fluid and hyperbaric bupivacaine (HB): a formulation with density heavier than cerebrospinal fluid (CSF). Hyperbaric bupivacaine 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.[3]

Several trials have shown that HB appears to cause more predictable sensory blockade than isobaric bupivacaine.[4] On the other hand, IB has been found to produce a longer duration of SA.[5 6] 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 vs. HB. [7] 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 GA or cancellation of surgery is required.

Trials, which have so far compared IB and HB, have not provided consistent results. Vernhiet et al 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.[8] Some studies have reported that the incidence of hypotension is higher with use of HB for spinal anesthesia. [9-13] On the contrary, others have reported similar incidences of hypotension, [14-17] or a lower incidence of hypotension with use of HB compared to IB. [18]

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,[9] however, others disagree.[6 19 20] Longer duration of motor and sensory block produced by IB has been proposed to be useful for longer surgical procedures.[21 22]

The side effects associated with SA include hypotension, bradycardia and intraoperative nausea and vomiting. The incidence of these side effects may be altered by the LA spread (or number) of nerve roots / segments blocked in 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 favorable side effect profile.[23-25]

This systematic review will summarize the best available evidence regarding the effectiveness and safety on the use of HB compared to IB, when used to provide spinal anesthesia for 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 spinal anesthesia.

Secondary Objectives:

2. 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.

3. 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 PRISMA-P guidelines. [26]

Criteria for considering studies for this review

Types of studies

We will include randomized 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 extremity. We will exclude patients undergoing emergency surgery or caesarean section.

Types of interventions

Included studies must have compared HB vs. IB introduced as a single shot SA. We will include only the studies that have used standard hyperbaric bupivacaine (i.e. 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 dose (mg) of LA will be excluded. We will also exclude studies, which included the elective use of general anesthesia (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 a 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 complete regression of motor block.

Search methods for identification of studies

Electronic searches

The following databases will be searched: PubMed (1980 to 31 Mar 2015), EMBASE (1980 to 31 Mar 2015), and the Cochrane Central Register of Controlled Trials (CENTRAL).

Search strategy is provided in appendix 1.

Selection of studies for inclusion in the review

Study selection will be performed in two stages, with two independent reviewers (VU, CP). At the first stage title and abstracts will be screened, followed by full text screening. Any discrepancy will be settled by mutual agreement or by an arbitrator (DM). We will calculate kappa scoring for agreement on full text study selection.

Data extraction

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

Assessment of risk of bias in included studies

We will assess the RoB using modified Cochrane RoB tool (reference). 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 risk of bias

Outcomes and Prioritization

We will prioritize intention to treat (ITT) approach, and consider complete case analysis for primary analysis. All studies using dextrose will be considered as hyperbaric bupivacaine, despite the variations within the dextrose concentrations. If there is more than a single group of either IB or HB, they will be combined into a single group for pooling and analysis. 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 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 program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; and Microsoft Excel program. Pooling will be done using a fixed effects model. However, if the I2 for a pooled outcome is >25%-indicative of significant inconsistency, we will analyze 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% confidence interval (CI). Measure of heterogeneity will be reported as Chi square (Chi2)-with a threshold of p set at 0.10, and inconsistency across studies as proportion of I2.

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 I2 statistic [27]. Measure of heterogeneity will be reported as Chi square (Chi2)-with a threshold of p set at 0.10, and inconsistency across studies as proportion of I2.

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 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 risk of bias component-by-component basis, only if there is considerable variability within the risk of bias component.

Subgroup and Sensitivity Analysis

Subgroup analysis

We will conduct a subgroup analysis for studies with lateral/unilateral block, vs. supine positioning, post spinal anesthesia. Surgeries needing unilateral spinal anesthesia, such as for amputation or lower limb surgeries may involve differences in drug volume and positional variation in the actions of spinal anesthetic. 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 risk of bias. We will conduct this subgroup analysis on a risk of bias component-by-component basis, only if there is considerable variability within the risk of bias component. This will be done only on the primary outcome.
2. Studies using Levo-bupicaine 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. [28] 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

Interpretation and Reporting

We will report our findings as RRs (dichotomous), and WMDs (continuous) for individual outcomes, along with their 95% confidence intervals. We will also report the findings in measures of relative risk 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. [3] 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 & International Anesthesia Research Society (IARS) meeting 2017) and anticipate high impact journal publication. Results disseminated on Social Media such as Twitter (@v.uppal, @dolores.mckeen) and tracked by Altametrics.

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

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Competing interests: None

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Appendix 1

We will use the following search terms to search all databases (modified to suit each specific database and employing the Cochrane highly sensitive search strategy).

The following search strategy will be used

1. Anesthetics OR Anesthesia OR Injections, Spinal OR bupivacine OR levobupivacinaine [Subject headings / MeSH] OR Anaesth* OR Anesth* OR sensorcaine OR marcaine OR popscaine OR bupivacaine OR levobupivacaine OR chirocaine OR subarachnoid* OR "neuraxial* OR intrathecal* OR block* OR Spinal* OR injection* [Freetext / keywords]

2. Hyperbaric OR glucose OR Dextrose [keywords]

3. Hypobaric OR isobaric OR plain [keywords]

4. Baricity

5. Cesarean Section [subject heading] OR cesarean-section* OR caesarean-section* OR c-section* [freetext / keywords]

Combined:

1 AND 2 AND 3

1 AND 4

2 AND 4

3 AND 4

NOT #5

No Date limits

No language limitations

Limited to Humans

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Methods and analysis: We will search key electronic database 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 randomized controlled trials, with no restrictions on language. Caesarean section surgery will be excluded. Two reviewers will independently extract the data using a standardized 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% confidence intervals.

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.

INTRODUCTION

More than 100 million surgical procedures are performed in USA and Canada each year.[1] Approximately, 5% or 5 million of surgical procedures are performed under spinal anesthesia (SA).[2] SA allows for an effective intraoperative anesthesia with good surgical conditions for surgeries on lower abdomen, pelvis and lower extremity. SA is performed by injecting a local anesthetic (LA) into the cerebrospinal fluid (CSF) in the subarachnoid space. This produces rapid-onset, intense sensory and motor blockade as well as sympathetic blockade.[3] Opioids, such as fentanyl, sufentanil, and morphine are sometimes co-administered 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 local anesthetic 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 cerebrospinal fluid and hyperbaric bupivacaine (HB): a formulation with density heavier than cerebrospinal fluid (CSF). Hyperbaric bupivacaine 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 isobaric bupivacaine.[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 vs. 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 GA or cancellation of surgery is required.

Trials, which have so far compared IB and HB, have not provided consistent results. Vernhiet et al 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.[9] Some studies have reported that the incidence of hypotension is higher with use of HB for spinal anesthesia. [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 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 favorable 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 summarize the best available evidence regarding the effectiveness and safety on the use of HB compared to IB, when used to provide spinal anesthesia for surgery. We are unaware of any previous 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 spinal anesthesia 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 spinal anesthesia.

Secondary Objectives:

2. 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.

3. 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 PRISMA-P guidelines. [27]

Criteria for considering studies for this review

Types of studies

We will include randomized 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 extremity. We will exclude patients undergoing emergency surgery or caesarean section.

Types of interventions

Included studies must have compared HB vs. IB introduced as a single shot SA. We will include only the studies that have used standard hyperbaric bupivacaine (i.e. 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 dose (mg) of LA will be excluded. We will also exclude studies, which included the elective use of general anesthesia (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 a 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 complete regression of motor block.

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 search

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 study which has not been published.

Search strategy is provided in appendix 1.

Selection of studies for inclusion in the review

Study selection will be performed in two stages, with two independent reviewers (VU, CP). At the first stage title and abstracts will be screened, followed by full text screening. Selection criteria will include: Randomised Controlled Trial; Adults (>18 years) having spinal anesthesia for non-Caesarean-section surgeries; Bupivacaine or Levobupivacaine used as Hyperbaric vs. Isobaric in at least 2 of the study groups. Performa for screening is attached as appendix 2. Any discrepancy will be settled by mutual agreement or by an arbitrator (DM). We will calculate kappa scoring for agreement on full text study selection.

Data extraction

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

Assessment of risk of bias in included studies

We will assess the RoB using 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 risk of bias

Outcomes and Prioritization

We will prioritize intention to treat (ITT) approach, and consider complete case analysis for primary analysis. We will include only the studies that have used standard hyperbaric bupivacaine (i.e. bupivacaine with glucose 80 mg/ml. If there is more than a single group of HB, the group with 8% dextrose with be compared to 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 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 program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; and Microsoft Excel program. 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 analyze 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% confidence interval (CI). Measure of heterogeneity will be reported as Chi square (Chi2)-with a threshold of p set at 0.10, and inconsistency across studies as proportion of I^2.

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 Chi square (Chi^2)-with a threshold of p set at 0.10, and inconsistency across studies as 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 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 risk of bias component-by-component basis, only if there is considerable variability within the risk of bias component.

Subgroup and Sensitivity Analysis

Subgroup analysis

We will conduct a subgroup analysis for studies with lateral/unilateral block, vs. supine positioning, post spinal anesthesia. Surgeries needing unilateral spinal anesthesia, such as for amputation or lower limb surgeries may involve differences in drug volume and positional variation in the actions of spinal anesthetic. 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 risk of bias. We will conduct this subgroup analysis on a risk of bias component-by-component basis, only if there is considerable variability within the risk of bias component. This will be done only on the primary outcome.
2. Studies using Levo-bupicaine 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 at 0.10, and I^2 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 subgroup analysis based on patient positioning soon after spinal anaesthesia, and also conduct sensitivity analysis based on studies with high risk of bias, 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% confidence intervals. We will also report the findings in measures of relative risk 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 & International Anesthesia Research Society (IARS) meeting 2017) and anticipate high impact journal publication. Results disseminated on Social Media such as Twitter (@v.uppal, @dolores.mckeen) and tracked by Altametrics.

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

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Competing interests: None

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Appendix 1

We will use the following search terms to search all databases (modified to suit each specific database and employing the Cochrane highly sensitive search strategy).

The following search strategy will be used

1. Anesthetics OR Anesthesia OR Injections, Spinal OR bupivacine OR levobupivacinaine [Subject headings / MeSH] OR Anaesth* OR Anesth* OR sensorcaine OR marcaine OR popscaine OR bupivacaine OR levobupivacaine OR chirocaine OR subarachnoid* OR "neuraxial* OR intrathecal* OR block* OR Spinal* OR injection* [Freetext / keywords]

2. Hyperbaric OR glucose OR Dextrose [keywords]

3. Hypobaric OR isobaric OR plain [keywords]

4. Baricity

5. Cesarean Section [subject heading] OR cesarean-section* OR caesarean-section* OR c-section* [freetext / keywords]

Combined:

1 AND 2 AND 3

1 AND 4

2 AND 4

3 AND 4

NOT #5

No Date limits

No language limitations

Limited to Humans

Appendix 2: Study Eligibility

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*
Language of abstract:
Language of full paper:

If answer to any of the following questions is NO, exclude the study and do not perform full text screening

Study Characteristics	**Eligibility criteria**	Yes	No	Unclear	**Location in text** *(pg & ¶/fig/table)*
Type of study	Randomised Controlled Trial	☐	☐	☐	
Participants	Adults (>18 yrs) having spinal anesthesia for non C-section surgeries	☐	☐	☐	
Types of intervention	Bupivacaine or Levobupivacaine used as Hyperbaric vs. Isobaric in at least 2 of the study groups. For hyperbaric-the study must have used only 8% Dextrose, and for Isobaric the study should not have used any Dextrose.	☐	☐	☐	
Single injection spinal	Only single shot spinals were included in study (Exclude continuous catheters or CSE)	☐	☐	☐	
Opioids	Was local anesthetic only used? (Please exclude if opioids or other adjuvants added to local anesthetic mixture)	☐	☐	☐	
LA dose	Was same dose of LA used in both groups? (Please exclude if different dose (mg) used in two groups)	☐	☐	☐	
INCLUDE ☐ **EXCLUDE** ☐ **UNCLEAR** ☐					
Reason for exclusion					
Notes:					

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable, original protocol (not amendment). Any amendments will be updated on PROSPERO
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 19
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable, Page 19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable, Page 19
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 10-11

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 11, The review will be coordinated from Department of Anesthesia, Dalhousie University. Data will be handled securely by storing it at the department research office. We will utilize electronic data extraction forms and well as paper forms depending on extracting authors preference. These forms along with the analysis will be handled securely at the research office, Dalhousie University.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 11 and Appendix 2
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 12-13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 13-14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 16-17. If quantitative synthesis is not appropriate, we plan to summarize the available evidence in a tabular form, presented as outcome tables for the primary and secondary

			outcomes considered in our review.
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 16-17

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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