PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	INTRATHECAL HYPERBARIC VERSUS ISOBARIC BUPIVACAINE FOR ADULT NON- CAESAREAN SECTION SURGERY: SYSTEMATIC REVIEW PROTOCOL
AUTHORS	Uppal, Vishal; Shanthanna, Harsha; Prabhakar, Christopher; McKeen, Dolores

VERSION 1 - REVIEW

REVIEWER	Ayten Saracoglu Istanbul Bilim University Medical School Turkey
REVIEW RETURNED	27-Dec-2015

GENERAL COMMENTS	The manuscript is well written. We will assess the RoB using modified Cochrane RoB tool (reference). Here the reference should be included.

REVIEWER	Sinan Uzman Haseki Training and Research Hospital, Deparment of Anesthesiology and Reanimation, Turkey.
REVIEW RETURNED	05-Jan-2016

GENERAL COMMENTS	There are numeous studies comparing the safety, effectiveness and characteristics of isobaric bupivacaine and hyperbaric bupivacine. But it is a controversial issue. I also believe that this comprehensive systematic review will help to aswer this question. I am looking forward to results.

REVIEWER	Sohan Lal Solanki Tata Memorial Centre, Mumbai-India, 400012
REVIEW RETURNED	23-Jan-2016

GENERAL COMMENTS	Thanks for inviting to review this protocol I am very happy to review the current systemic review protocol for intrathecal hyperbaric versus isobaric bupivacaine for adult non-caesarean section surgery. The methodology is exhaustive and systematic; ethics approval is taken and registered in clinical trial registry. Data analysis and statistical methods are satisfactory. I will love to see and review the final results and manuscript whenever this study will be completed. All the best for this study

REVIEWER	Faraj Abdallah University of Toronto, Canada
REVIEW RETURNED	05-Feb-2016

GENERAL COMMENTS	Thank you for the opportunity to review this systematic review protocol. The Design and Methods described are sound; I have few minor comments. Abstract: 1. Suggest including the terms “intrathecal” and “subarachnoid” in the search strategy. 2. Search strategy should also include the term “surgery”, otherwise the search will retrieve a lot of unnecessary items, such as “spinal anesthesia for brachytherapy” for example. 3. Please provide a justification for limiting the search date to 1980. 4. Please specify the general outcomes sought (the measures of effectiveness and safety) Introduction: 1. Please have one coherent paragraph on side effects. P7 L3-16 can be combined with P6 L28-42. 2. The rationale can be strengthened; the current presentation suggests an academic interest rather than a real clinical problem that the authors are attempting to address. The reason why is it important to conduct this review needs to be more convincing. 3. Has there been any earlier systematic reviews addressing the same question? Please specify. 4. Please clarify the position on additives upfront (in the introduction), as these may affect the outcomes sought (efficacy and side effects). 5. A few words on how spinal anesthesia works would be helpful, as the journal and its readership are not necessarily anesthesia-oriented. Methods: 1. Definition of failure: Please be more specific as to how you will handle i) repeated spinal injections and ii) supplementation (e.g. opioids). 2. The authors want to search the Medline database, not Pubmed. 3. Suggest including trial registries for completion of search (clinicaltrials.gov, EU Clinical Trials Register and Current Controlled Trial Register). 4. Suggest inclusion of abstracts of meetings for completion of search. 5. Selection strategy: Please specify the criteria for selection of studies. 6. Outcomes and prioritization: The approach to managing differences in the measurement of the primary outcome should be mentioned here. (e.g. variations in how success / failure of spinal are defined in the reviewed trials). Same applies for how spinal regression is assessed. 7. Any plans for dealing with missing data? 8. What is the plan for exploring sources of heterogeneity?

REVIEWER	Dr Victoria Allgar University of York, England
REVIEW RETURNED	22-Feb-2016

GENERAL COMMENTS	This is a well written protocol for this proposed systematic review, which outlines the approach that will be undertaken. However, it is just a protocol and contains no data or analysis. This paper should be resubmitted once the review had taken place and report the findings. As it stands I'm not sure it will be of interest to readers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Ayten Saracoglu, Istanbul Bilim University Medical School Turkey

The manuscript is well written.
We will assess the RoB using modified Cochrane RoB tool (reference). Here the reference should be included.
Response: Thanks for pointing out. The reference has been included.

Reviewer: 2

Sinan Uzman, Haseki Training and Research Hospital, Deparment of Anesthesiology and Reanimation, Turkey.
There are numerous studies comparing the safety, effectiveness and characteristics of isobaric bupivacaine and hyperbaric bupivacine. But it is a controversial issue. I also believe that this comprehensive systematic review will help to answer this question. I am looking forward to results.
Response: no changes requested.

Reviewer: 3

Sohan Lal Solanki, Tata Memorial Centre, Mumbai-India, 400012

I am very happy to review the current systemic review protocol for intrathecal hyperbaric versus isobaric bupivacaine for adult non- caesarean section surgery.
The methodology is exhaustive and systematic; ethics approval is taken and registered in clinical trial registry. Data analysis and statistical methods are satisfactory. I will love to see and review the final results and manuscript whenever this study will be completed.
All the best for this study
Response: no changes requested.

Reviewer: 4

Faraj Abdallah, University of Toronto,

Thank you for the opportunity to review this systematic review protocol. The Design and Methods described are sound; I have few minor comments.

Abstract:
1. Suggest including the terms “intrathecal” and “subarachnoid” in the search strategy.
Response: the terms intrathecal and subarachnoid have been included in our search strategy

2. Search strategy should also include the term “surgery”, otherwise the search will retrieve a lot of

unnecessary items, such as “spinal anesthesia for brachytherapy” for example.
Response: We appreciate the thoughtful comment. However, we have not included the term surgery in search as we want the search to be more inclusive. We will hand search and exclude all non-relevant trials.

3. Please provide a justification for limiting the search date to 1980.
Response: We have removed date restrictions from search strategy. This has been reflected in the manuscript “We will search Medline, Embase and Cochrane databases, from their inception for randomized controlled trials, with no restrictions on language.”

4. Please specify the general outcomes sought (the measures of effectiveness and safety)
Response: We have specified the following primary and secondary outcomes for our review. Primary outcome is “number of patients needing conversion to general anesthesia”. Our secondary outcomes are incidence of clinically significant hypotension, incidence of nausea-vomiting, and the measured duration of anesthesia. For all our outcomes, we have established clear definitions.

Introduction:
1. Please have one coherent paragraph on side effects. P7 L3-16 can be combined with P6 L28-42.
Response: the two paragraphs suggested by the reviewer have been merged to form one coherent paragraph.

2. The rationale can be strengthened; the current presentation suggests an academic interest rather than a real clinical problem that the authors are attempting to address. The reason why is it important to conduct this review needs to be more convincing.
Response: We have added a statement about clinical problem that the review will address “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.” We have focused on the clinical and patient relevant outcomes. This will allow clinicians to make meaningful decisions on the choice of medication.

3. Has there been any earlier systematic reviews addressing the same question? Please specify.
Response: We have added a line “We are unaware of any previous published systematic review addressing this question.”

4. Please clarify the position on additives upfront (in the introduction), as these may affect the outcomes sought (efficacy and side effects).
Response: In introduction section, we have added a line at the end of first paragraph - 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”. We have also made it clear in the methods section that we will be excluding trials in which an additive has been used, as they lead to clinical, and potential statistical heterogeneity.

5. A few words on how spinal anesthesia works would be helpful, as the journal and its readership are not necessarily anesthesia-oriented.
Spinal Anesthesia 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. A text book reference has been added.

Methods:
1. Definition of failure: Please be more specific as to how you will handle i) repeated spinal injections and ii) supplementation (e.g. opioids).
Response: A repeat injection has the potential to cause high spinal blockade and can potentially

influence study outcomes. However, we do not expect a large number of repeated injections within a single study. We also expect the investigators to use the same type of injectate (either isobaric or hyperbaric), even with repeat injections. If a study reports >10% of patients as having had repeat injections, we will do a sensitivity analysis on the primary outcome of “needing to convert for general anesthesia”. With regards to non local anesthetic supplementation (additives), we have earlier stated that those studies will be excluded.

2. The authors want to search the Medline database, not Pubmed.
Response: We apologize for this inadvertent error. This has been corrected in the manuscript

3. Suggest including trial registries for completion of search (clinicaltrials.gov, EU Clinical Trials Register and Current Controlled Trial Register).
Response: We will conduct this search as suggested, and cross check with our search results. Further, we will contact investigators for study reports of any completed study which has not been published. We have incorporated these statements in our methods section.

4. Suggest inclusion of abstracts of meetings for completion of search.
Response: As part of the study selection, we will include both full text, and study abstracts. We will report the study characteristics and important study conclusions in a table. However, for our meta-analysis we will only include full study reports. It has been observed that reporting of study results in abstracts is poor (Eur J Anaesthesiol 2011; 28: 485–492). We also will not be able to assess the study quality and other important characteristics appropriately.

5. Selection strategy: Please specify the criteria for selection of studies.
Response: Selection criteria will include: Randomised Controlled Trial; Adults (>18 years) having spinal anesthesia
for non C- section surgeries; Bupivacaine or Levobupivacaine used as Hyperbaric vs. Isobaric in at least 2 of the study groups. Performa for screening has been attached as appendix 2.

6. Outcomes and prioritization: The approach to managing differences in the measurement of the primary outcome should be mentioned here. (e.g. variations in how success / failure of spinal are defined in the reviewed trials). Same applies for how spinal regression is assessed.
Response: We have stated definitions for our outcome measures as follows: Failure rate of SA, assessed as either the need for conversion to GA, or as cancellation of surgery. Incidence of intraoperative hypotension: defined as the need for use of vasopressors. 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. Onset time: defined as the time from the performance of SA to the time when patients were deemed suitable for the start of surgery. Time to complete regression of motor block.
Any variation in the above definitions in individual publications will be reported in the results

7. Any plans for dealing with missing data?
Response: Since our study outcomes are captured within the same day, we do not anticipate any loss to follow up. If a study does report >20% missing data for our outcomes, we will do a sensitivity analysis.

8. What is the plan for exploring sources of heterogeneity?
Response: This has been clarified in methods section: Statistical heterogeneity will be calculated using Cochrane’s Q test, with a threshold of p value 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.

Reviewer: 5

Dr. Victoria Allgar, University of York, England

This is a well written protocol for this proposed systematic review, which outlines the approach that will be undertaken. However, it is just a protocol and contains no data or analysis. This paper should be resubmitted once the review had taken place and report the findings. As it stands I'm not sure it will be of interest to readers.
Response: No changes requested. We think the reviewer has misunderstood. We are intending to publish this protocol in BMJ open.

VERSION 2 – REVIEW

REVIEWER	Sohan Lal Solanki Tata Memorial Centre, Mumbai-India
REVIEW RETURNED	29-Mar-2016

GENERAL COMMENTS	Can be accepted

REVIEWER	Faraj Abdallah University of Toronto, Canada
REVIEW RETURNED	12-Apr-2016

GENERAL COMMENTS	Thank you for involving me in reviewing the updated protocol. The authors have done a good job addressing reviewers' comments and incorporating the suggested changes.