Author's response to reviews

Title: The effects of spinal anaesthesia for elective caesarean section on uterine and umbilical arterial pulsatility indexes in normotensive and chronic hypertensive pregnant women: a prospective, longitudinal study.

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Author's response to reviews: see over
Cover Letter

Name of Corresponding Author: Luís Guedes-Martins, MD
Manuscript Title: The effects of spinal anaesthesia for elective caesarean section on uterine and umbilical arterial pulsatility indexes in normotensive and chronic hypertensive pregnant women: a prospective, longitudinal study.
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Dear Editors,

BMC Pregnancy & Childbirth

Please find attached a revised version of our manuscript ‘The effects of spinal anaesthesia for elective caesarean section on uterine and umbilical arterial pulsatility indexes in normotensive and chronic hypertensive pregnant women: a prospective, longitudinal study,’ which we are resubmitting for publication as an original article in BMC Pregnancy and Childbirth. Your comments were highly insightful and enabled us to greatly improve the quality of our manuscript. The following pages detail our point-by-point responses to each editorial comment.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Pregnancy and Childbirth.

We look forward to hearing from you at your earliest convenience.

Sincerely,

Signature

Date

Aug 03, 2014

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CopyEdit:
I would recommend that the authors copyedit the manuscript to improve the syntax and grammar. I have made a number of suggestions, but there is a need to review the text in detail throughout the manuscript to improve readability. Please seek out external input to improve the copyediting.

Response: As suggested, the manuscript was copyedited by the editing service Edanz to improve readability.

Improvements are also still required for data presentation, especially for the figures (which require major revision).

Response: The data presentation and figures were improved consistent with the editorial ‘Specific comments.’

Lastly, there are important limitations that need to be highlighted - see specific comments. Although there are a number of revisions that are still needed, I think these issues are minor and can be probably overcome with one further round of revision. I apologize for the number of comments. The intention is to help not hinder. Many of these are to do with syntax/grammer. Specific comments:
Remove ‘an observational study?’ from the title.

Response: This has been done.

P3L67: Please add: ‘did not change after spinal anesthesia?’ if correct.

Response: This has been done.

P3L68: Insert comma after women

Response: This has been done.

P4L87-88: The description for the etiology of spinal hypotension needs to be improved. Based on studies assessing changes in maternal cardiac output and central hemodynamic indices, a marked reduction in maternal systemic vascular resistance occurs which means that arteriolar dilatation as well as aortocaval compression are key etiologic factors. Please edit the text to reflect current up to date scientific data on the etiology of spinal hypotension. Remove references 15-18 and replace with the following (more accurate) references from landmark papers which provide highly important data on changes in maternal cardiac indices post-spinal anesthesia:
Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology 2008; 109: 856?63

Response: The text was edited and the corresponding manuscripts were cited as suggested.

P6L130: Add text to indicate that the N/REF is the IRB protocol number. It is not clear in the current form.

Response: This has been done.

P6L133: Please do not abbreviate gestational age. Change all abbreviations to full text in the manuscript.
Response: This has been done.

P6L150: Please indicate which provider (Obstetrician/Ultrasonographer) performed ultrasounds.
Response: This has been done.

P7L151: the text indicating that the obstetrician reviewed ?patient?s history?, etc? is superfluous. You already stated the inclusion/exclusion criteria. Remove relevant text from lines 152-154.
Response: This has been done.

P7L155: state specifically what neonatal assessments were performed by the neonatologist.
Response: The newborn physical assessment included: Apgar scoring, birth weight, head circumference, abdominal circumference, length, vital signs (temperature, pulse, and respiratory rate), general appearance, and physical and neuromuscular maturity. This information was added to the revised manuscript.

P7L157: Change ?installation of anesthetic blockade? to placement of spinal anesthesia. Then start a new sentence to state that. The upper level of dermatomal block between T4-T6 tested by ? was determined to be adequate for surgical anesthesia. Replace ? with method of testing ie. Ice/cold/pinprick/light-touch.
Response: This has been done.

P7L158: Remove the sentence starting ?It included?.. As you go into later detail in the methods section on these measurements.
Response: This has been done.

P7L167: As clinical assessment of the level of spinal anesthesia is notoriously inaccurate, simply state that ?the block was performed at a mid-lumbar level?.
Response: This has been done.

P7L168: spelling. Change to through
Response: This has been done.

P7L170: Start the sentence with: ?Spinal anesthesia consisted of 8-9 mg hyperbaric bupivacaine?..
Response: This has been done.

P7L171: remove ?according to patient?s characteristics?..
Response: This has been done.

P7L172: remove sentence starting ?an epidural catheter??this is superfluous.
Response: This has been done.

P7L174: Move the sentence about method of testing the block up?.see earlier comment on testing the spinal block.
Response: This has been done.

P8L184: State here what vasopressor you used ? ephedrine.
Response: This has been done.
P8L191: change to ???.before and after spinal anesthesia?.

Response: This has been done.

P8L194: add the initials of the study investigator who performed the ultrasound examinations. Add a sentence to indicate his/her level of ultrasound expertise.

Response: This has been done.

P8L197: Did the authors have any BP criteria (e.g. 20% decrease in SBP from baseline) for administering vasopressors? If not, then this should be highlighted in the limitations section as BP treatment was not standardized across groups.

Response: The standard for vasopressor (VP) administration was defined as a 20% decrease below the baseline mean arterial pressure at any time post-induction. This information was added to the ‘Blood pressure assessment’ section (Methods). I wish to emphasize that the study only included cases that did not require VP before the second time point (Doppler measurements were performed after spinal anaesthesia). However, many of these patients required VP immediately after the second measurement or during the post induction. Thus, we have not established any relationship between the uterine artery Doppler measurements and future VP administration. In our opinion, this relationship would not make sense.

What was the average timeinterval between timepoints? This would be useful to know to ascertain how soon the second timepoint was measured.

Response: Unfortunately, this interval was not recorded. Regardless, no more than 15 minutes elapsed between the time points. This is a study limitation that was rigorously discussed in the revised manuscript.

P9L203: Please provide details for the manufacturer’s software for deriving PI values.

Response: This has been done.

P9L219: Recommend delete sentence starting ?multiple linear regression had to be considered? as vague and arguably superfluous.

Response: This has been done.

P10L224: Time cannot be considered a dichotomous variable. For the purposes of your model, your description should state that it was a fixed variable presumably with before spinal as the reference state (as your description was before vs after [see line 245]) as opposed to a continuous variable.

Response: The explanatory variables in a regression model are not random variables. They are indeed observed realizations of the true variables. Thus, the modelling of the response is always for the conditional distribution, given the explanatory variables value. However, it is common practice to use the term variables. In our study, time (actually the hypertensive status) could only take one of two, possible values and was therefore an explanatory dichotomous variable. We were interested in comparing the index values before anaesthetic blockade to those values obtained afterwards. Were the study design simpler (e.g., no other confounding variables to control for), we would have simply performed a regression of the index values over time (before/after), which would require a t-test. In our situation, the model estimation considered time as a single dummy variable representing the state after anaesthetic blockade.

We apologize, but the authors do not agree with this particular editorial recommendation; therefore, we wish to maintain the sentence.
Table 1: Display age, BMI as continuous data either mean (SD) or median [IQR]. Display parity as median [IQR]; revise P value for relevant data (t-test or Mann-Witney U test). For categorical data, simply display %s for those with the condition ? smoking, UA bilateral notching.

Response: This has been done.

Table 2 and 3: Delete asterisk and text explaining p value inference. This is superfluous.

Response: This has been done.

P13L307: Please clarify what you mean by ?indicative?. This term is not intuitive to understand.

Response: This has been done.

P13L309: Remove sentence starting ?the correspondent models?. Descriptions for the statistical analyses belong in the methods section ? not the results section.

Response: This has been done.

Figures 1 and 2. As outlined in the original review, the figures should be improved. As previously recommended, display the data in box plots for each group at each time point.

Response: Box plots are now inserted and legends reviewed.

Add text for each variable to indicate the reference groups e.g., after spinal anesthesia (reference group = before spinal anesthesia); hypertension (reference group = non-hypertensives)

Response: This has been done. These reference categories were included in Tables 4 and 5 to improve clarity.

P14L322: Display data for the UtA-PI and U-PI models in tabular format (as per Table 4). The purpose of the model in Table 5 in not clear, esp. as the models for each pulsatility index is previously described. Is this model necessary? what is the outcome variable ? pulsatility index is non-specific- for this model?
Please provide data for the AIC values (as described in L262).

Response: We thank the editor for raising this concern.
Table 5 summarizes the results of the model fitting (1) described in the Statistical Analysis section. The modelled artery is captured by the variable v in model equation (1). The modelling of PIs in uterine (UtA) and umbilical (U) arteries are performed simultaneously. This is because the UtA-PI and U-PI are highly correlated, and a separate modelling would bias the results; this procedure is similar to several two-by-two comparisons, instead of multiple comparisons all in once. The variable v (vessel) is dichotomous and has UtA as the reference category; the variable h (hypertension) is dichotomous and has the non-hypertensive group as its reference category; and time is dichotomous and has the period before the anaesthetic blockade as its reference category. These reference categories were included in the table to improve clarity. As the expression U-PI in the explanatory variables might cause misinterpretation, it has abbreviated by U.

P15L354: ?Inappropriate? is a poor descriptor. Consider ?compromised blood supply to the fetus?.

Response: This has been done.

P15L359: It is unclear if the BP decrease is more prominent in the HT group. To ascertain this, values for the MAGNITUDE of change are needed (% change) for each group. These data are not currently shown in the paper.

Response: Thank you for your suggestion.
The model equation for MAP predicts values for different combinations of time and hypertensive status (Figure 1 and Table 4), namely: before spinal anesthesia, normotensive group: 83.1 (95% CI: 81.8–84.5), hypertensive group: 105.5 (95% CI: 102.2–108.9); and after anesthesia, normotensive group: 76.2 (95% CI: 75.5–77.0), hypertensive group: 94.5 (95% CI: 92.6–96.5). In particular, the model predicts an 8.3% decrease in the mean MAP within the normotensive women and a 10.4% decrease in the hypertensive women.

This data was added to the results section (MAP model).


Response: This has been done.

P17L393: Spinal hypotension is occurs commonly so this occurrence is not surprising. I would be inclined to omit text on this as you excluded patients who received vasopressors from your study, so any comment on this is purely speculative.

Response: As suggested, the text was omitted.


Response: This has been done.

P17P433: What specifically do you mean by ?disbalance between the groups?. Please be more specific with regard to what disbalance is present and why this impacts on the modeling.

Response: The sentence was clarified in the Study limitations and future research section (5).

P17: Note that you did not assess neonatal outcomes in detail. This lack of data must be included as an important limitation in the discussion, as the clinical relevance of your findings remains uncertain.

Response: This aspect is now pointed out in the study limitations and future research section (6).

In addition, only two time points were assessed, therefore an acknowledgement that further time-dependent changes in PI indices cannot be ascertained from the results of your study. This is touched upon in the last paragraph of the discussion, but should be moved up to the limitations section.

Response: This has been done. This point was discussed in the Study limitations and future research section (7).

It is unclear whether your findings translate to patients with pre-eclampsia, superimposed pre-eclampsia or gestational hypertension. This must be highlighted as an important limitation in your discussion, esp. as this was flagged during the original peer review process.

Response: This has been done. This point was discussed in the Study limitations and future research section (1).

Lastly, the incidence of spinal hypotension can be up to 70% Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand 2010; 54: 909?21), therefore the use of vasopressors is relatively common. As patients who received vasopressors were excluded, this limitation is important and it is unclear if the PIs vary among women who develop spinal hypotension and receive vasopressors compared to those who do not develop hypotension.

Response: This has been done. This point was discussed in the Study limitations and future research section (4).

P17L441: remove ?coursing?
Response: This has been done.