Author's response to reviews

Title: The effects of adding epinephrine to ropivacaine for popliteal nerve block on the duration of postoperative analgesia: a randomized controlled trial

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Author's response to reviews: see over
Re: The effects of adding epinephrine to ropivacaine for popliteal nerve block on the duration of postoperative analgesia: a randomized controlled trial

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Dear Dr. Rowles,

Thank you for the evaluation of our revised manuscript and for the constructive comments made by the reviewers.

Below, the comments made by the reviewers are repeated verbatim in parentheses, our reply in blue. In the revision, all changes are delineated by bolded text. We believe that we have addressed all issues raised by the reviewers adequately and hope you will agree.

Thank you once again for your trouble; we look forward to your reply.

On behalf of all authors:
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Sincerely,

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**Reviewer’s report**: Stephen Choi

**Major compulsory Revisions**

Thank you to the authors for the response to our comments, they address many of the issues that were brought up.

1. The authors and I will have to agree to disagree regarding the rationale for excluding patients who did not make a request for additional analgesics in the study period being removed from analysis and replaced with new participants.

From the other reviewers’ comments, it appears both Dr. Dillane and I agree in this respect that this is a methodologic concern and one in which block duration and TTFR are not the same outcome although the authors used TTFR as a surrogate for block duration. By the authors own definition of block failure (page 7, line 121) no request for analgesia (even up to 48h) should be considered a block success. Since the authors appear to have collected both outcomes, TTFR and duration of sensory/motor block, perhaps they should have been presented separately.

We apologize for the confusion that has risen due to the lack of clarity of our previous answer. In our first response to the question about exclusion of the patients who did not make a request for additional analgesics, we did not intend to state that they were excluded because of block failure;

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the blocks were definitely successful, but since in these two patients the primary outcome parameter TTFR was missing and at 48 h the sciatic nerve block had worn off, we felt it would have been inappropriate to include these patients in the analysis of block duration with a value of 48 h.

It seems that in our previous answer as well is in the Methods’ section of our manuscript we have not made sufficiently clear that the offset of the sciatic nerve block was not measured in a similar fashion as the onset. The reason for this choice was both practical and ethical: Measuring the offset of a sciatic nerve block would imply frequent measurements at regular intervals, and since we used ropivacaine, its long duration of action would have meant frequent measurements during nighttime. We considered this unacceptable, and therefore we chose to use the TTFR as the primary outcome parameter to reflect the duration of sensory block instead.

If patients had made no request for postoperative analgesia at $t = 24\text{h}$ and in the presence of (partial) sciatic sensory block, the observation period was extended to $t = 48\text{h}$. If at 24h or 48h patients had made no request and in the absence of (partial) sensory sciatic nerve block, the block was successful, but they were replaced because of absence of the primary outcome parameter and consequently the inability to determine or estimate block duration.

In order to make this clear to the reader and to avoid misinterpretation or confusion, we have adjusted the text in the Methods’ section on page 7 lines 121-122, lines 124-129 and 131-135, as well as in the Results’ section on page 9, lines 170-171.

Despite the explanation given above we appreciate that our decision to replace the two patients who had not made a request for analgesia and no signs of persisting sciatic nerve block at 48 h raises concern, since the sciatic nerve blocks in these patients were obviously successful. We therefore incorporated a statement addressing this issue in the Discussion on page 12, lines 229-234.

2. Page 5, line 84: Why were anesthesiologists performing the block procedure not blinded? There is no reason for this. It can only serve to create bias.

We agree with the reviewer that whenever blinding is possible, it is preferable over awareness of treatment allocation. However, all blocks were performed by experienced anesthesiologists in a standardized fashion as described in the treatment protocol. Since they were not involved in block assessment or in any other way in the conduction of the study, we believe that the absence of blinding of the anesthesiologists performing the blocks does not affect the results.
3. Response letter page 3, point 2: The authors state ‘surgery was started before the onset of block and patients were operated under general anesthesia with long acting opioids’. This is inconsistent with the study protocol page 5/6 lines 95 to 98 where it states that surgery was performed under regional alone, GA only for surgery > 120 minutes with no mention of long acting opioid. This is a major difference in protocol - which was performed because it could materially change the results and subsequent interpretation.

We understand the concerns raised by the reviewer and also here we apologize for our lack of clarity. There was no major difference in protocol: The two patients the reviewer is referring to were withdrawn before the start of surgery. Due to OR logistics, both patients whom this concerns went to the OR immediately after block performance and before the first block assessment could be made. In the absence of an effective sciatic nerve block the attending anesthesiologist of the first case decided not to wait for the onset of sciatic nerve block, but to administer general anesthesia including the administration of sufentanil, in the second case the attending anesthesiologist made the same decision. Since general anesthesia with sufentanil would constitute a protocol violation, the independent observer responsible for block assessment made the decision to withdraw these patients from the study before surgery, and the study protocol was consequently abandoned. To make this clear, we have adjusted the text in the Results’ section, page 9 lines 174-178.

4. Page 6 line 104-107: Where is the data regarding opioid use?

The study protocol ended at the TTFR of ropivacaine and per hospital protocol patients were allowed to receive morphine 0.1-0.15 mg/kg every 4h subcutaneously as needed thereafter. Because the study protocol ended with TTFR, and before any opioid administration, we did not collect these data as they bear no relevance to the objective of our study.

Reviewer’s report: Sanjiv Patel

Discretionary Revisions

Any more information on potential side effects including those specifically related to the use of adrenaline.

On page 9 lines 180-181 have been adjusted to: None of the patients showed signs of local anesthetic systemic toxicity or inadvertent intravascular injection of epinephrine (such as rise in heart rate, systolic blood pressure or flushing).

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