Author's response to reviews

Title: Gabapentin and postoperative pain; A qualitative and quantitative systematic review, with focus on procedure.

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Author's response to reviews: see over
Dear Editor

Please find attached the revised manuscript entitled: “Gabapentin and postoperative pain; A qualitative and quantitative systematic review, with focus on procedure”

The revisions are:

- A paragraph has been added to the Discussion, concerning the matter of interpretation of the use of PCA morphine as primary outcome measure in light of different VAS-pain measures in the treatment and placebo groups.
- A paragraph has been added to the Discussion, mentioning the lack of dose-response effect in the included trials.
- Spelling errors regarding American vs. British spelling has been corrected.

The following pages contain our reply to comments of the reviewers.

We believe that the revision has improved the manuscript and hope that it is acceptable in its current form.

Yours sincerely

Ole Mathiesen, MD
Comments on review on the manuscript

Henry McQuay
“the primary outcome measure is PCA opioid consumption, with simultaneous VASPI or equivalent. The assumption is that patients in the active and control treatment groups will titrate ‘down’ to the same low VASPI, and the difference in opioid consumption at SAME VASPI gives us the valid difference in opioid consumption. This simply doesn’t happen in all except 3 of these trials. From my hypercritical standpoint the rest of the trials are invalid and should not be included in the analysis.”

Authors reply:
We agree with Dr. McQuay that this is a limitation in the review and have added a small paragraph to the Discussion concerning this point.

“The absence of mention of dose-response”

Authors reply:
Again we agree that this topic merit space in the Discussion, and have added a small paragraph describing the one trial addressing this topic.
Frederick Burgess
“*A few spelling errors may need to be addressed.*”

Authors reply:
We have corrected the errors found, except for Page 14 line 9: “favour”, as we believe this is the correct British spelling.
Alparslan A Turan

“I suggest authors to report about procedure specific data and delete the remaining, it is just repeating of available information from other metanalysis”

Authors reply:
We understand the reviewer, but have to say that we disagree. In our review we have included 7 more trials than the last published review on this topic, and we believe that the inclusion of these allows for a more updated review, as well as the qualitative and quantitative analysis in the review both is important contributions to a more complete review.

“Last sentence of the first paragraph needs to be rewritten”

Authors reply:
We wrote:
“Opioid analgesics, with their well-known side-effects, continues to represent a cornerstone in postoperative pain control, and testing new analgesics as well as combinations of analgesics in order to reduce the need for opioids, is a key area in acute pain research.”
We disagree and have not changed this paragraph.

“Last sentence of second paragraph needs to be written again, and there is some error like ‘central sensibilisation’”.

Authors reply
We wrote:
“In pain models it has shown anti-hyperalgesic properties, possibly by reducing central sensibilisation, a prerequisite for postoperative hyperalgesia, and gabapentin, together with dextromethorphan and ketamine, represents a new option in postoperative pain care, which recently has been the subject of intensive research.”
and have changed “sensibilisation” for “sensitization”. Otherwise we don’t find that the sentence have to be rewritten.

“12 and 16 trials are not about postoperative pain and opioid usage.”

Authors reply:
Reference 12 by Jadad et al, is about a quality score of randomized trials, and is a background article for the review.
Reference 16 by Leung et al, addresses the use of gabapentin for postoperative delirium. It also investigates the effect of gabapentin on postoperative pain, but since it contains < 10 patients, we have not included this trial in our analyses.
“Hypothesis needs to be more clearly written”

Authors reply:
We wrote:
“An increasing number of randomised trials indicate that gabapentin is effective as an postoperative analgesic. Until now, four meta-analyses with pooled data from rather few studies (7, 8, 12 and 16 trials, respectively) [6-9], demonstrates that gabapentin displays an effect on both postoperative pain score and opioid usage. In these meta-analyses, data from studies with very different surgical interventions are pooled and therefore the effect in a particular surgical setting is difficult to predict. We find that the recent number of publications allows a more procedure-specific systematic review in this area, which is the purpose of this paper.”
-and have not changed this.

“It will be nice if authors can compare difference between 1h and 2h prior application of gabapentin”

Authors reply:
We have to say that we do not feel able to make this comparison.