Author’s response to reviews

Title: General vs. neuraxial anaesthesia in hip fracture patients: A systematic review and metaanalysis

Authors:

Julia Van Waesberghe (jvanwaesberg@ukaachen.de)
Ana Stevanovic (astevanovic@ukaachen.de)
Rolf Rossaint (rrossaint@ukaachen.de)
Mark Coburn (mcoburn@ukaachen.de)

Version: 1 Date: 23 Mar 2017

Author’s response to reviews:

Dear Hisham Hosny, dear Iain Moppett, dear Carlos Luis Errando,

Thank you very much for your helpful comments and giving us the chance to revise our manuscript. We addressed all points raised by the Editor and by the Reviewers, see below. We are looking forward to your response. Thank you very much.

Yours sincerely

Mark Coburn

1.Iain Moppett (Reviewer 1):

a)I have repeated the search in Pubmed and retrieved 465 articles. Can the authors explain this discrepancy?
Response:

Thank you for coming up with this point. We checked the search-strategy by ourselves and retrieved 465 hits as well. We cannot explain this discrepancy. However, we screened the additional papers and adapted the flow chart and the systematic review accordingly.

b) Most systematic reviews now include some element of forward searching (citations), 1 or 2 level reference list searching, and formal searching of trial registries. I'd be surprised if other studies were found, but I would suggest this should be done for completeness.

Response:

Thank you for your advice. We performed a forward searching in google scholar, a 1 level reference list searching and a formal searching of trial registries for all included studies. The formal searching of trial registries was performed with clinicaltrials.gov and the “ICTRP Search Portal” of the World Health Organization. We could include one study (Chu and colleagues) due to the additional search.

c) There is a study missing - White et al 2016. (I say this as one of the authors - and I have attached it to this review). This does raise doubts about the effectiveness of the search / retrieval strategy (it is found by the PubMed search). The results of this study are almost identical to the findings of the authors, so its inclusion is probably not going to change the conclusions.

Response:

After repeated PubMed search, we have now identified your study and included it in our systematic review.

d) Inevitably I have checked the data for one of my studies and these are not correct. White 2014 (p 226) - The MS (figure 2) has n/N of 1345/23665 for spinal - this should either be 1713/23665 (all spinal) or 135 / 18955 (spinal only (not with block); similarly the data for GA are wrong - given as 1066 / 35373: should be either 1066/15666 (GA only) or 2112/31092 (all GA) or 2393/35372 (GA + (GA+SA)). I haven't checked any others bar Neuman (which is correct).
Response:

Thank you for your advice. This is a transmission error. We adapted the numbers it in the script and double-checked the values in the meta-analysis of all other studies.

e) I am unclear as to how GA+RA was managed in the analyses. I don't think there is a 'right' answer. It would seem prudent to repeat the analyses with and without this group. There is some suggestion that the combined GA/SA group might do worse.

Response:

There are only the two studies of White and colleagues and the study of Patorno and colleagues, which defined an extra group for general anaesthesia combined with regional anaesthesia. Due to the limited number of studies it is not meaningful to repeat the analysis with and without these groups. For the mentioned studies we included only the values for general and regional anaesthesia alone.

f) Risk of bias: a minor point, but the risk of bias has been put as high for the Parker trial as participants knew their allocation. This is probably a little harsh for a mortality outcome, and realistically also for length of stay.

Response:

Thank you for your advice. You are right. We changed it in the paper accordingly.

g) Exclusion of Neuman study for length of stay. Although the Neuman study doesn't include a direct SD is it estimable from the CI given in the paper. The authors question their own analysis due to the heavy weighting of the Helwani study, so it would seem sensible to try to include the Neuman study. The White 2016 study showed no difference between the groups so this might alter the overall conclusion.
Response:

Now, we have included the Neuman study in the meta-analysis for the length of hospital stay and calculated the standard deviation with the formula: $SD=\sqrt{N \times \text{(upper limit-lower limit)/3.92}}$. Additionally, we could include three further studies (White et al., Chu et al. and Heidari et al.), which changed the result of the meta-analysis. The length of hospital stay is now significantly shorter in the neuraxial anaesthesia group.

h) There were 4 studies excluded at full text - please elaborate.

Response:

We have checked the four excluded studies and reconsidered to include the study of Neuman and colleagues and Heidari and colleagues, see above. The study of Zhao and colleagues was excluded, because the authors do not define what “local” anaesthesia means. The study of Basques and colleagues was excluded, because the values for postoperative length of stay were not usable for our systematic review. His first aim was not to compare general with regional anaesthesia. They wanted to identify factors associated with an increased length of stay after hip fracture surgery. However, with including the aforementioned studies we could enlarge the meta-analysis for the length of hospital stay and in-hospital mortality.

i) It would support the robustness of the study if the authors provided sensitivity analyses - eg. excluding small studies, etc.

Response:

Thank you for your advice. We performed our meta-analyses with the RevMan program. This program weights the studies amongst other criteria by their size and their quality of values. We do not think that it is disadvantageous for the analysis to include the small studies. If we would exclude the small studies the meta-analyses would even be smaller. Yet we mention this now in the limitations section.

2. Carlos Luis Errando, PhD (Reviewer 2)

a) As per "definition of inclusion criteria", perhaps the manuscript would be better described (and entitled) 'general vs regional neuraxial anesthesia', instead of '...regional anesthesia'.
Response:

Thank you for your advice. We changed the title of the systematic review in “general vs. neuraxial anaesthesia”.

b) Important outcomes other than mortality were not addressed, as pulmonary embolism, cardiac or respiratory complications, etc.

Response:

Now we have included a secondary outcome section in the review for the postoperative incidence of myocardial infarction, pneumonia and pulmonary embolism.

c) It can be criticized that studies included a wide age range of patients, instead of only elderly patients (a more outcome-centered population, for instance >65 year-old). However it can be argued that this depends on the original studies included.

Response:

Our first idea was to write a systematic review, focused on the elderly population. However, the literature is sparely. Therefore we decided to include all studies with a patient age ≥ 18 years. Nevertheless, hip fracture occurs predominantly in the elderly. If we would have included only studies with an inclusion age ≥ 65 we would have a significant drop-out rate.

c) Please report homogeneously the author’s citation along the text, i.e. Shih and colleagues (reference),... not ...and others.

Response:

We altered the author’s citations accordingly.

d) Page 3, line 59-60: it is unclear to which population these number refer to (worldwide population? population quoted in one of both references?)
Response:
We modified the citation in the text.

e) Page 4, lines 71-72: ref 24 lacks

Response:
We added reference number 24 in the text.

f) Page 7, lines 139-142: please modify, ...sample sizes in the included studies varied widely, the largest one including 73284 patients (ref), and the smallest one 45 patients (ref).

Response:
We modified your comments in the text.

g) Line 145: ...confounding factors (refs).

Response:
We altered your comment in the text.

h) Line 146: ...a high risk of bias, because...

Response:
We modified your comment in the text.

i) Point 3.3: perhaps this paragraph would offer better comprehension if reported as a table only (with a brief introduction at the start of the paragraph)
Response:
Thank you for your note. We altered the section in the text.

j) Page 9, lines 173 and following: please rewrite. We performed a separate subgroup analysis of the ten retrospective observational studies and the two RCT studies.

Response:
We modified your comment in the text.

k) lines 183-184: ...Shih and colleagues (n=335,...); the same in lines 193 and following (Le-Wending and colleagues. patorno and colleagues,...)

Response:
We adapted the author´s citations accordingly.

l) Page 11, line 213: ...There was no heterogeneity

Response:
We altered your comment in the text.

m) Page 13, line 254: ...furthermore only 2152 patients...

Response:
We adapted your comment in the text.

n) line 255: ...difference, instead of ...disction (mistake ??)
Response:

This was a spelling mistake. We meant “difference” instead of “disction”.

o)Page 14, line 256: ...included, instead of ...concluded

line 262: anaesthesia groups

Response:

We modified your comment in the text.

p)Some references are incorrectly reported:

Ref 1: web page? please report following Instructions for authors
Delete month in references: 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 22, 23, 24, 26, 28, 29, 30, 31, 32, 33

Response:

Thank you for your advice. We rework the reference list.

q)ref 18, please rewrite

Response:

We correct reference number 18.

r)ref 25, 152-7
Response:
We modified your comment in the text.

s)ref 26: change capital letters

Response:
Thank you for your advice. We revised the reference list.

t)ref 29: 323-30

Answer:
We altered your comment in the text.