Author's response to reviews

Title: Comparison of the effectiveness of low pressure pneumoperitoneum with profound muscle relaxation during laparoscopic donor nephrectomy to optimize the quality of recovery during the early post-operative phase: study protocol for a randomized controlled clinical trial

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Author's response to reviews:

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Dear Editor,

We thank the reviewers for their useful comments. Below a point-by-point response to the comments of the reviewers.

Referee 1:

1.a) Why will the surgeon be informed of treatment allocation if the pressure is maximised? This will remove blinding. Will these patients be removed from the trial?

Reply: In case of insufficient peri-operative conditions, first intra-abdominal pressure will be increased. When, despite standard intra-abdominal pressure, peri-operative conditions remain insufficient, the surgeon will be informed that intra-abdominal pressure cannot be increased, and he should decide if further action is required (e.g. conversion to hand-assisted or open). At this stage, the surgeon is not informed about the initial pressure (i.e. low or standard pressure). We apologize for the confusion and changed the manuscript (page 6, line 157-160).

b) How will they be analysed? If they are removed will you increase the sample size to account for this?
Reply: All analyses will be performed on an intention to treat basis (please see page 9, line 235). When intra-abdominal pressure is maximized, these patients will not be removed from the analysis.

2. Please provide further detailed description of the post-operative treatment protocols - e.g. analgesia and pain assessment protocols, post-operative feeding etc. Will these be standardised between groups (they need to be). What are the criteria for discharge?

Reply: We thank the reviewer for his/her suggestion and we provided more detailed information in the methods section on this issue.

We added: “On day 0 postoperative pain will be assessed every 4 hours (during daytime), thereafter pain will be assessed every 8 hours” (page 7, line 168-169).

We also added: “On day 0 patients are offered a liquid meal, thereafter patients are encouraged to eat regular meals (page 7 line 169-170).

And we added: “Since the spouse or child of the patient is frequently the recipient of the donor kidney, patients are often longer admitted then strictly medically necessary. Therefore, the following discharge criteria will be daily assessed: 1) satisfactory pain management with oral analgesia, 2) occurrence of flatulence and faeces, 3) ability to walk on the ward and 4) ability to wash and change clothes independently (page 7, line 175-179).”

3.a) Statistical analysis: much more detail is required here. How will the stratification criteria be adjusted for in the analysis? I cannot see any justification for a 10 point difference being clinically relevant in the reference given. This is a key point since it is the primary outcome. What does a 10-point difference actually mean for the patient?

Reply: This is indeed a highly important issue. Although it is difficult to speculate on the precise impact of a 10 point difference, four other studies regarded a 10 point difference as the minimal clinically relevant difference. These references were added to the methods section (page 8, line 228). Moreover, an improvement in the quality of recovery is directly related to patient satisfaction. Also there is a relationship between quality of recovery in the days and weeks after surgery, with quality of life up to 3 years after cardiac surgery. We added this to the methods section (please see page 7, line 183-187).

3.b) Why have you chosen post-operative day 1 as being most important?

Reply: We agree that this should be clarified. We have chosen QoR-40 at day 1 as primary outcome measure since we expect the most distinct difference between low and standard intra-abdominal pressure on day 1. This is in line with other studies that also observed the greatest difference in QoR-40 at postoperative day 1. This was added to the Method section (page 7, line 186-187).

3.c) Will you account for gender in the analysis since the QoR-40 values are
different for males and females in many studies? Further the SD is different for males and females and is not 15 in either males or females according to reference 14. Statistical input is needed for this trial.

Reply: We agree that gender differences for QoR-40 is a relevant issue. Myles et al found that SD was higher for women as compared to men. The QoR-40 on day-1 for mixed types of surgery, ranging from ambulatory to major surgery, varies between 12 and 23. As in our study a very homogeneous patient population will be recruited (i.e. healthy kidney donors), we believe that a standard deviation of 14 is justified. We clarified this issue in the methods section (page 9 line 229-232).

4. Competing interests: please provide further detail of this relationship and in particular the role of the funder in study design, data collection, analysis and reporting.

Reply: This is an important issue and we clarified that the funder will not have any role in data collection, data analysis or reporting. This is added to the manuscript (page 11, line 284-285).

5. Background: Paragraph 3: your pilot study (only 1 author involved in pilot study and this protocol) is mentioned as reference 7, yet later on in Methods your pilot is referenced as reference 6 (no joint authors). This requires clarification.

Reply: We apologize for this confusion. The pilot study should be reference 7, this is changed in the manuscript (page 8, line 212). Michiel Warlé and Frank d’Ancon(a) whom are also authors of the current manuscript) co-authored the pilot study.

6. Methods: Will you stratify for age and is there any need to?

Reply: We agree with the reviewer that this is also a relevant issue, post-operative pain can be influenced by age. In our center the vast majority of live kidney donors is between 40-60 years old. This was also confirmed in our previous pilot study (mean age 50±10). Given this relatively small range, stratification for age is not strictly required in our view. We clarified this in the manuscript (please see page 5, line 109-110).

7. Adverse events: please also include monitoring for adverse events to the deep neuromuscular blockade and sugammadex

Reply: We thank the reviewer for his her suggestion and we added information to the methods section: “To monitor neuromuscular blockade, TOF measures will be assessed every 10 minutes during the procedure. To avoid residual paralysis, necessitating prolonged stay on the post-anesthesia care unit, sugammadex will be administered. Patients will only be extubated when TOF is > 90%. Furthermore, patients will stay at the post anaesthesia care unit for 2 hours, to ensure adequate neuromuscular function” (please see page 8, line 219-224).
8. Sample size: what about patients who withdraw and those who are unblinded. Will unblinded patients be included in the analysis. Will the sample size be increased to account for these?

Reply: When peri-operative conditions are inadequate and intra-abdominal pressure is increased, the surgeon will not be informed of the allocation of treatment. We addressed this issue in response to question 1. Therefore these patients will be analyzed on an intention-to-treat basis and the sample size will not be increased.

Since the primary outcome measure is on postoperative day 1, we expect the number of drop-outs is minimal. However when patients drop-out before randomisation, they will be replaced.

9. Methods: exclusion criteria: please define creatinine as upper level of normal.

Reply: The upper limit is creatinine level of 201 micromol/l (this was added to the manuscript, page 6, line 128)

10. Following sentence 'as' should read 'and'.

Reply: We apologize for this error and changed the manuscript accordingly (page 6, line 129).

11. Study protocol: paragraph 4: Has the SRS been used by more than 1 previous study? If so please provide detail as further justification for the use of this tool.

Reply: To our knowledge the SRS has not been used in more than 1 previous study. However, there is no validated method of evaluating peri-operative conditions for laparoscopic surgery. The SRS in the trial by Martini et al. was assessed by eight surgeons, specialized in laparoscopic surgery, an average statistic of 0.50 was found, indicating moderate agreement between the surgeons. Currently a validation study of subjective rating scales to assess surgical conditions in laparoscopic surgery is being performed (NCT02079337). We added this issue to the discussion section (page 10, line 269-2670).

12. Discussion: paragraph 1: consider changing 'optimizes' to 'improves'

Reply: We thank the author for his/her suggestion and changed the manuscript accordingly (page 9, line 243).

Referee 2:

1. The study investigators will be blinded to the allocation group but I’m not certain that blinding will be easily achieved. The concern is that experienced surgeons are likely to know when a low pressure pneumoperitoneum is being used because the abdominal cavity will be flaccid. Deep neuromuscular blockade may obviate this but further reassurance is needed on this point.
Reply: We agree with the reviewer that it might be possible that in some cases the surgeon might guess whether low or standard pressure pneumoperitoneum is used. During our pilot study, in most cases the surgeon was not certain which pressure was used. We are, however, not aware of a method further optimizing blinding of the surgeon. At the end of surgery, the surgeon will be asked whether low or standard pressure was used. Therefore, at the end of the study, we can evaluate the efficacy of the blinding process. This issue was addressed in the discussion section (page 10, line 262-265).

2. a) I am not personally familiar with the surgical rating score (SRS) depicted in Table 1 but this seems fairly subjective. It would be more robust if more than one observer scored this aspect.

Reply: We agree with the referee that the SRS is a subjective score. However, to date there is no validated method of evaluating peri-operative conditions for laparoscopic surgery. Currently a validation study of subjective rating scales to assess surgical conditions in laparoscopic surgery is being performed (NCT02079337). We addressed this issue in response to question 11 of reviewer 1 and have added this to the discussion section (page 10, line 266-270).

b) Presumably a poor view due to problems with the laparoscopic camera will be excluded as causes of poor visibility – this should be mentioned.

Reply: We agree, this was added to the manuscript (page 6, line 151-153).

3. I wasn’t sure why the surgeon would be unblinded if the SRS does not improve to >3 after increasing the pressure to 12 mmHg. Why not leave the surgeon blinded and allow him to proceed as he feels necessary i.e with conversion to hand assisted or open? Why let him know what the starting pressure was?

Reply: We also addressed this issue in response to question 1 of reviewer 1. The surgeon will not be informed about the initial pressure. We apologize for the confusion and changed the manuscript ( page 6, line 157-160).

4. The sample size has been informed by a power calculation but the sample is rather small (n=64). The sample size was designed to detect a 10-point difference in the overall score using the quality of recovery 40 (QoR) scale at post-op day 1. The authors state that this difference is clinically relevant and reference a paper by Myles PS et al (ref 14) to support this. I can’t find mention of the relationship between the QoR score and clinical relevance in the quoted paper. This is important because recovery from laparoscopic nephrectomy is already good and this suggests that a large sample would be required to show a meaningful improvement with low pressure pneumoperitoneum.

Reply: We fully agree and already addressed this issue in response to question 3c of reviewer 1, please also see page 9 line 229-232.

All requests from the editor are changed in the manuscript. We thank you for
your time and consideration.

Kind regards,

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