Author’s response to reviews

Title: Effects of Low Versus Standard Pressure Pneumoperitoneum on Renal Syndecan-1 Shedding and VEGF Receptor-2 Expression in Living-donor Nephrectomy: A Randomized Controlled Study

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Author’s response to reviews:

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Editorial Department of BMC Anesthesiology

Dear Editors,

Please consider our revised manuscript, entitled “Effects of Low Versus Standard Pressure Pneumoperitoneum on Renal Syndecan-1 Shedding and VEGF Receptor-2 Expression in Living-donor Nephrectomy: A Randomized Controlled Study” for publication in BMC Anesthesiology. We appreciate the interest that the editors and reviewer have taken in our manuscript and the constructive reviews they have given to improve our manuscript. We have addressed the concerns of the reviewer.

We have also included a point-by-point response to the reviewer in addition to the changes described in the manuscript. We have revised and made the discussion section more concise.

Thank you again for consideration of our revised manuscript.
Yours Sincerely,

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POINTS OF REVISION:

Reviewer #4

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable
OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?

&gt;&gt;Maybe - with major revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The authors did a great job in adapting the paper to the reviewers' comments. Unfortunately, I did not see the previous version of the paper being invited to review only the present one. So, I have some further comments which need to be addressed.

ADDITIONAL REQUESTS/SUGGESTIONS:

Specific comments:

Introduction: extremely well written.

Response:

Thank you for your review and assessment

Materials and methods: extremely well written.

Response:

Thank you for your review and assessment

Results - lines 298-9: I think "comparable" is not enough. I would change into "non-statistically significant differences in…".

Response:

Thank you for your suggestion, we have revised it accordingly:

We change comparable into “…non-statistically significant difference in…” (page 14, line 312)

Results: I would specify in the text if the pneumoperitoneum pressure was kept stable along the whole procedures or if temporary increase were necessary to keep up with surgical needs. Although live donor nephrectomy is not a bloody procedure, pneumoperitoneum pressure increases is common practice during specific steps of other procedures associated significant
bleeding (e.g., tumor resection in minimally-invasive partial nephrectomy or DVC section and suture in minimally-invasive radical prostatectomy). Clarification is needed. The fact that the patients were randomized to pressure of 8 or 12 mmHg does not mean that that pressure was not increase due to specific reasons during the procedure due to surgical needs.

Response:

We add data to clarify the stability of the pressure on:

- Table 3. Intraoperative data: Pneumoperitoneum pressure stability (page 14–15, line 321–325)

- We add: “The 12 mmHg group showed intraoperative pressure stability in 14 patients and pressure loss during suctioning or instrumentation in 8 patients that needed intermittent pneumoperitoneum pressure increase, which significantly different than the 8 mmHg group that showed the pressure stability in 3 patients and pressure loss in 19 patients. None of the subjects analyzed had a significant bleeding during the procedure that needed pneumoperitoneum pressure increase.” (page 14, line 314–319)

Results: intraoperative and postoperative overall and high-grade complication rates should be reported somewhere in one of the tables.

Clarification:

- None of our subjects analyzed had complications of subcutaneous emphysema, or pneumothorax

- Need of additional port, conversion to open laparotomy, failure to maintain low pressure would be excluded from the study (drop out criteria)

We stated: “Exclusion criteria were hemodynamic instability defined as the changes of mean arterial pressure or cardiac index &gt; 25% below or above baseline despite intervention treatment, significant bleeding causing failure to maintain pressure, and conversion of laparoscopy to open nephrectomy.” Page 7, line 169–172)

- We reported intraoperative and postoperative data including one-year follow up separately in Table 3: Patients intraoperative and postoperative data. (Page 14–15, line 321–325)

Results: level of precision of the results is inaccurate. Please, see https://doi.org/10.1016/j.eururo.2014.06.024.
Clarification:

- We revised the level of precision of the results according to: Vickers AJ., Sjoberg DD. Guidelines for Reporting of Statistics in European Urology. European Urology 67 (2015): 181–187, as suggested:

- “All baseline and perioperative characteristics are presented in Table 1. Sex, age range, BMI, baseline BUN and creatinine levels were not significantly different between the two groups. (Page 12, line 296–298)

- We revised: “Categorical variables are presented in n (%). Numerical variables are presented as mean (± standard deviation) or median and confidence interval 95% (minimum–maximum), p&lt;0.05 is significant. The two groups were compared with Chi-Square Test or unpaired t-test or Mann-Whitney U test.” (Page 13, line 300–302)

- We revised:” Table 2 shows that hemodynamic cardiac index (CI), stroke volume index (SVI), mean arterial pressure (MAP), and end-tidal CO2 were not significantly different between the 12 mmHg and 8 mmHg groups. However, heart rate (HR) in the 12 mmHg group was significantly higher than…” (Page 13, line 304–308)

- We revised: “Table 3 shows the non-statistically significant difference in the duration of pneumoperitoneum, surgery, anesthesia, warm and cold ischemic time, and postoperative urine output between the two groups.” (Page 14, line 312–314)

- We revised: “Categorical variable presented in n (%). Numerical variable presented with median and confidence interval 95% (minimum–maximum), p&lt;0.05 is significant. The two groups were compared with Fisher test or Mann-Whitney U test. (Page 15, line 323–325)

- We explained the Figure 2 in the discussion (page 15–16, line 327–357) and Figure 2 caption with the data are presented as geometric mean and confidence interval 95% (minimum–maximum) depends on the repeated ANOVA for continuous data, and using unpaired t-test and a general linear model for between-group comparisons.

- We explained the Figure 3 in the discussion (page 16, line 361–366) and Figure 3 caption with the data are presented as median (95% CI) since the two groups were compared using Mann-Whitney test.

- Figure 3 discussion we change from comparable into “The H-score of syndecan-1 expression in the distal tubules was non-statistically significant different between the 8 mmHg and 12 mmHg groups” (page 16, line 363–364)

- We explained the Figure 4 in the discussion (page 17, line 370–374) and Figure 4 caption with the data are presented as median (95% CI) since the two groups were compared using Mann-Whitney test.
- Figure 5 discussion we change from similar into “Peritubular arterial endothelial cell VEGFR-2 expression was not significantly different between groups. (page 17, line 377)

- We explained the Figure 5 in the discussion (page 17, line 374–379) and Figure 5 caption with “Artery VEGFR-2 expression score is not significantly different between groups “ and the data are presented as median (95% CI) since the two groups were compared using Mann-Whitney test.

Results: I am not familiar with the CO2 insufflator produced by Olimpus and used in the present study but the vast majority of the insufflator that I saw/used in Europe do not allow the keep the intraabdominal pressure always stable during the procedure, especially whenever suction is needed or laparoscopic instruments are inserted. To my knowledge, the only device working in a different way is the AirSeal System by Conmed. This pressure barrier insufflator works by creating and maintaining a forced gas pressure barrier in the proximal end of the trocar with a system of continuous pressure flow (inflow and outflow) to create a valveless pressure curtain rather than the standard one-way valve system. This new generation of valve-less and barrier-free surgical trocars are typically associated with extremely stable pneumoperitoneum pressure along the procedures, despite suction and instruments insertion. Clarification is needed on this issue. The fact that the patients were randomized to pressure of 8 or 12 mmHg does not mean that that pressure was stable at that values during the procedure. It should be reported if such variations were recorded or that should be disclosed as a limitation.

Clarification:

- We used standard pneumoperitoneum insufflator Olympus Medical System Corp, UHI-4, Tokyo Japan (page 9, line 199–200), not the AirSeal System.

- We add data to clarify the stability of the pressure on: Table 3. Intraoperative data: Pneumoperitoneum pressure stability (page 14–15, line 321–325)

- We add: “The 12 mmHg group showed intraoperative pressure stability in 14 patients and pressure loss during suctioning or instrumentation in 8 patients that needed intermittent pneumoperitoneum pressure increase, which significantly different than the 8 mmHg group that showed the pressure stability in 3 patients and pressure loss in 19 patients.” (page 14, line 314–318)

- We add: “The limitation of this study is the use of a standard CO2 pressure insufflator which does not allow to keep the intraabdominal pressure always stable during the procedure, especially during suctioning or insertion of laparoscopic instruments, that was overcome by intermittent increase in CO2 insufflation pressure.” (page 24, line 546–549)
Discussion: still too long and wordy. A paragraph with the study limitations should be included at the end. The authors data are very elegant but renal function at follow-up was similar in both groups. So, either all the observed differences are not clinically significant in the long term or the study is underpowered to detect such differences.

Clarification:

- We have reduced the length of discussion from 1942 words into 1618 words.

- We add limitation of the study: “The limitation of this study is the use of a standard CO2 pressure insufflator which does not allow to keep the intraabdominal pressure always stable during the procedure, especially during suctioning or insertion of laparoscopic instruments, that was overcome by intermittent increase in CO2 insufflation pressure. It is also important to evaluate the risks and benefits between low and standard pressure in operator’s point of view related to operative comfort such as space for dissection, and vision while using suction. From the one year follow up, all the observed differences are not clinically significant in the long term because of the study is underpowered to detect those differences.” (page 24, line 546–553)