Author's response to reviews

Title: Epoetin administrated after cardiac surgery: effects on renal function and inflammation in a randomized controlled study

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Author's response to reviews: see over
Dear Editor,

We are pleased to submit a revised version of our manuscript entitled “Epoietin administrated after cardiac surgery: effects on renal function and inflammation in a randomized controlled study” to the BMC nephrology journal. We thank the referees for their review.

We have provided a detailed response to the specific reviewers’ questions below. In summary, we have added information on the power calculation of our study. We have also modified the tables and the figures, as well as the discussion. We believe that our manuscript has been improved by these changes.

We hope that you will now find it acceptable for publication in BMC nephrology.

Best regards,

Patrick Saudan MD, PD
Point by point answers to the referees:

Referee one.

We thank the referee for his helpful review and comments.

1. Major revisions:
   The standard deviation of the change in urinary NGAL values at 48 hours was 110ng/ml precluding any possibility of highlighting a statistical significant difference with our limited number of patients. This is now stated in the text.

B.

Based on the figure 1 in the study of Mishra et al. Lancet 2005, where children with AKI had at 48 hrs an increase of 75 ng/ml (SD +/- 50 ng/ml) in mean urinary NGAL and no increase in those without AKI, we extrapolate that the mean urinary NGAL increase at 48hrs in our adult patients with AKI would be similar but in those without AKI would be higher than in children without AKI (on account of their previous comorbidities) and we arbitrarily define a mean increase of 30 ng/ml in this group. We were expecting to have an effect size of one SD between our control and Epo-treated group, which gave us a power of 0.95 with an alpha of 0.05. We chose urinary NGAl values as the primary endpoint to calculate our sample size, assuming that a calcul based on creatinine measurements (a less sensitive marker of subtle renal dysfunctions) would need a too large population.

C. We corrected the tables 2 and 3 to include the absolute values (median and interquartiles) instead of differences or log value. We consolidated figures 2 and 3 to avoid redundancy with the corrected tables and now show the differences in renal biomarkers in one figure (figure 2). We corrected the units used for cytokines.

Referee two:

We thank the referee two for her very careful review and interesting comments.

Major:

1-3. We agree that they are many available data showing that NGAL peaks at 4-6 hours, after cardiac surgery, and decreases thereafter. However, according to Mishra et al. the differences between uNGAl in AKI versus non-AKI patients are still very significant during the days following cardiac surgery. We also made the same observation at 48h in our study as shown in the corrected table 3.
We administered Epo after cardiac surgery. Therefore, we would not expect to modify the first peak in uNGAL by our therapy. We however postulated that Epo treatment would either induce a more rapid decrease in uNGAL and/or that it would avoid progression of renal injury or prevent secondary injury that may occur after ICU admission. We therefore analyzed the changes of renal biomarkers between the follow-up period and randomization, as well as the absolute values. All values were not significantly modified by EPO therapy.

We agree that baseline measures of uNGAL would have been useful to interpret the uNGAL values at randomization. Unfortunately, we were unable to collect them because of the many restrictive requests of our national drug control organ limiting inclusion before surgery.

4. Although the study is described as "open label" in the registry, the randomization occurred as described in the text under the methods section. The information in the registry is therefore incorrect and we apologize for that.

5. As requested we have collected intraoperative values such as length of the cardiopulmonary bypass, timeliness of the operation (elective vs urgent), presence of vasoconstrictors or inotropes and transfusions administered (table 1). No difference between the groups was noted and this is now shown in table 1. Unfortunately, we have not been able to obtain the exact fluid balance and hemodynamic variables, but patients were all managed according to a published protocol to which we now refer in the text (Licker, M et al. Annals of Cardiac Anaesthesia Vol. 15:3 Jul-Sep-2012).

6. AKI was diagnosed from admission to the 96h after ICU admission. We also confirmed that no patient developed AKI after the first week (p6). Patients were excluded at enrolment if diuresis was less than <600 ml/12 hour as described in the methods section but, not those with milder forms of AKI.

8. See the answer to referee 1.

Minor:

1. We added serum creatinine as requested in table 3.
2. The flow diagram has been completed according to the CONSORT checklist and we corrected the number of screened patients (386 instead of 432). No patient was excluded after enrollment. The eligible patients that were not randomized did not wish to participate in the study. Only 1 patient (in the EPO 20000ui group) was transferred after 48h to another hospital but did neither develop AKI nor other complications.
3. We added the year of enrollment as requested.
4. We added a sentence on Endre study in the discussion as requested
5. The timing of uNGAL measurement was added to the abstract.
6. We corrected the sentence accordingly
7. Seven patients received contrast medium before surgery: 1 in the placebo group, 2 in the EPO 20000 group and 4 in the EPO 40000 group (p=NS). Only 2 of these patients in the EpO group developed AKI (p=NS). This information has been added to the text (p 6)
8. Hb levels during follow-up is now provided in table 2 and a sentence states the they are no differences between treatment groups.

Referee three:

1. We modified the introduction and stated that present data do not support Epo use in humans, as suggested by the referee.
2. Low dose Epo reduced uNGAl compared to the high dose group, there were no significant differences with the control group. This is discussed in the results section and clarified with the addition of a figure (figure 2c).