Author's response to reviews

Title: OPAL: Randomized, controlled clinical trial to investigate oxygen persufflation as adjunct in liver preservation

Authors:

Thomas Minor (tminor@uni-bonn.de)
Carolin Pütter (Carolin.puetter@uk-essen.de)
Anja Gallinat (a.gallinat@gmx.de)
Claudia Ose (Claudia.Ose@uk-essen.de)
Gernot Kaiser (Gernot.Kaiser@uk-essen.de)
Andre Scherag (Andre.Scherag@uk-essen.de)
Jürgen Treckmann (j.treckmann@gmx.net)
Andreas Paul (Andreas.Paul@uk-essen.de)

Version: 3 Date: 13 October 2011

Author's response to reviews: see over
Dear Sir!

Please find enclosed the revised manuscript of our study protocol entitled:

‘OPAL: Randomized, controlled clinical trial to investigate oxygen persufflation as adjunct in liver preservation’,

submitted for publication in Trials.

We are thankful for the referee’s remarks and we tried to meet the suggestions. A list with point by point answers to the reviewer’s comments is attached.

We hope that the revised manuscript will now be acceptable for publication in your esteemed journal and we are looking forward to hearing from you in the near future.

With best regards
Yours,

T. Minor
Answers to the review:

Thank you for considering this study as interesting and rigorous.

1. Due to the particularities of organ transplantation it is in fact the incoming liver, which is randomized by our study design. This randomization is stratified according to the MELD-score of each individual participant, to whom every single liver has previously been allocated independent from our study. Only livers, which were allocated to patients who had given informed consent to participate in the study will be included in the randomization and the study. The study team discuss to adjusting for more patient-level strata, but on the one hand the MELD-Score is the most important strata and on the other hand too much strata could increase the possibility of prediction. Concealment of allocation is guaranteed as the randomization is performed by an webbased validated randomisation system (including audit trail) which means that each liver will have a equal chance of being allocated to either the oxygen persufflation or standard arm procedure that enter the randomization process. This procedure should remove all biases or confounding effects related to liver properties.

In agreement with the German law on organ transplantation, no grafts retrieved after cardiac arrest will be obtained or transplanted. The inclusion criteria for the donor liver were set as to confine the study to the category of ‘less than optimal’ grafts, which might show the highest proclivity to preservation injury and thus take benefit from the experimental treatment. The homogeneity in this group is relatively close. However, donor liver characteristics like cold ischemia time or degree of liver steatosis are routinely monitored and will be available upon analysis.

2. In our opinion it seems unethical to include sham pinpricks in the standard procedure, which then would no longer be a standard procedure. Moreover, side effects, however improbable, related to the presence of pin pricks would not be as easily be attributed to the treatment group. We do not think, however, that the lack of blinding the surgeon will have a notable impact on the primary endpoint, i.e. the serum transaminase levels after transplantation which is an objective measurement less susceptible to subjective influences (biases due to open studies have been shown to have a larger effect if the outcomes are subjective).

3. All serious adverse events or outcome events must be reported by the study coordinator Prof. Dr. Minor within 7 days using the Serious Adverse Event form. Forms are in the investigator site file. The investigator at the site Essen and Prof. Dr. Minor have to assess if this SAE was (likely to be) caused by the transplantation and/or oxygen persufflation. This SAE will be sent to the IEC by Prof. Minor. The DSMB will receive twice a year a list of SAE and complications. Cases of death will reported without delay to the DSMB. This procedure is in line with the Declaration of Helsinki.

4. In the abstract we were not able to give more verbose explanations on enhanced criteria donors and the magnitude of the problem of using less than optimal preserved donor organs for transplantation, due to the restriction of abstract word count. We however tried to enlarge the paragraph in the manuscript introduction concerning the rising clinical problem of enhanced criteria for acceptance of donor livers (e.g. donor age over 65),...
increasing use of steatotic livers for transplantation and the deterioration of liver quality upon extended times of organ preservation.

The passus on venous systemic oxygen persufflation and the preclinical valuation of the mot appropriate time period of treatment has been rewritten as to better describe the matter in more detail.

5. Inclusion criteria: donor age over 65 represents the most pertinent enhanced donor criterion for liver transplantation, associated with higher risk of poor graft function upon reperfusion. It was therefore taken as inclusion criterion for the study, which is primarily aimed to improve the fate of those livers with higher risk of primary dysfunction.

6. We are thankful for the comment on the exclusion of patients with present (actually means current) alcohol or drug abuse. As this criterion according to current clinical practice, actually excludes any patient from being transplanted at all, we have deleted this item from our list of exclusion criteria specific for the present study.

7. Serum peaks of liver transaminases still represent the most commonly used parameters for the progression of liver related disease. They correlate well with parenchymal graft injury associated with initial liver dysfunction after transplantation and are most often used as readout in clinical studies. In considering the serum levels during a period of three days it is thought that a more robust basis will be obtained for the judgment of the individual liver under investigation. If this proceeding is also useful to address the skewness of the AST distribution is an open question but we proposed non-parametric test statistics to address this issue. Other parameters, like e.g. 3-month mortality or rate of re-transplantation have a low incidence, even in the intended collective of ‘less than optimal’ livers, that seriously lessen the probability that the treatment effect will reach statistical significance in face of the limited number of patients chosen for a first proof of concept study.

8. We have extended the description on the sample size calculation by indicating what a relative effect of $p=0.66$ implies in terms of an average (location) shift in standard deviations of a standard normal distribution (assuming a parametric model – t-test with equal variances).

9. This paragraph has been rewritten.

10. We agree that more missing data in the control arm might result in a more favorable claim for the experimental arm; in this case, however, interpretation of the results will be difficult to impossible any way. No imputation strategy or replacement will be best suited here. The only way to deal with this question is continued quality control and quality assurance to address missing data issues during data collection and honest reporting after data base freeze. We have extended the paragraph accordingly also describing the Behrens-Fisher problem.

11. We apologize for the typographical errors in the manuscript, which we tried to correct in the present revision.