Author’s response to reviews

Title: Epicardial delivery of autologous atrial appendage micrografts during coronary artery bypass surgery - safety and feasibility study

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Revision comments:
Reviewers’ reports:

Reviewer #1: This pilot and feasibility study appears eminently reasonable.
Right atrial appendage tissue can be harvested without harm to the patient at the time of CABG.
The methods are clearly described and the pilot study is not of any ethical concern
Authors’ reply: We are grateful for the Reviewer’s positive comments on our manuscript.

Reviewer #2:

1. Please provide specific primary and secondary objectives for the trial (which link to the primary and secondary outcomes), in particular relating to how this study will inform a future trial.

Authors’ reply:

We thank the Reviewer for pointing out this important issue with our manuscript. We have now added the following text to the Introduction (page 8, line 6-14): “The primary objective of this trial is to evaluate the clinical feasibility of intraoperative harvesting, processing and transplantation of autologous atrial appendage tissue micrografts in terms of success in completing the delivery of the transplant to the myocardium in conjunction with cardiac surgery in the operating room as well as in terms of time restrictions associated with both transplant processing and cardiac surgery. Our primary objectives, in terms of safety, are to evaluate acute and 6-month cardiovascular parameters including rhythm, cardiac function and need for vasoactive or inotropic medication. Our secondary objective is to obtain an initial insight into the therapeutic effect of atrial appendix micrograft transplantation as measured by baseline and 6-month-follow-up cardiac functional MRI.”

We have also added a table of the outcome measures to further clarify the aims and outcomes of the trial (Table 2). (Page 12, line 5)

2. What criteria will be used to determine the success of this study, i.e. in relation to progression to a future trial?

It appears that the allocation of patients to either intervention or control is not randomised. How then is the decision made on whether recruited patients are selected for the intervention or control?

Authors’ reply:

The purpose for this study is to address patient safety and clinical feasibility of the therapy. We determine the success of this trial based on the primary outcome measures. If the therapy will be proved safe without any disturbances in patients’ cardiac rhythm, hemodynamics and cardiac
function and the method can be successfully performed simultaneously with bypass surgery, the results of this trial are then further evaluated in succeeding trials for transplant’s therapeutic efficacy. Double blind randomization and placebo control using the matrix-sheet with and without the micrografts will be considered for our future studies. (Page 15, line 1-8)

The allocation of the patients is not randomized. Patients are recruited to the groups in chronological order; first 6 patients are recruited to the intervention group and the following 20 to the control group (Page 10, line 11 and 15, Page 11, line 4)

3. Authors should discuss the limitations (for example, relating to selection bias and imbalance between treatment groups) resulting from the non-randomised nature of the trial.

Authors’ reply:

As suggested by the Reviewer, we have now added the following paragraph to the manuscript text:

“This study on feasibility and safety of autologous atrial micrograft epicardial transplantation has some limitations. The allocation is not randomized and the patients are recruited to the groups in chronological order. Also this trial is carried out as a one-center trial and therefore the number of eligible patients is small. Although randomization does not occur we have considered that no selection bias will take place due to low number of patients and because all patients who are eligible and give their consent are included in the study.
(Page 15, line 15-20).”

4. Please provide an accompanying SPIRIT checklist (reporting guidelines for trial protocols found at SPIRIT). (http://www.spirit-statement.org/)

Authors’ reply: We agree with the Reviewer and thank for the constructive suggestion to utilize and include the SPIRIT checklist to the protocol.