Minutes of Cardiothoracic Transplant Clinical Trials Meeting

Board Room, Royal College of Surgeons of England

2nd November 2015 11:00-14:00

Attendees: Nicholas Banner, Harefield
Pedro Catarino, Papworth
Dave Collett, NHSBT
Matthew Fenton, Great Ormond St Hospital
Peter Friend, Oxford
Diana Garcia, Harefield
Nagarajan Muthialu, Great Ormond St Hospital
Jasvir Parmer, Papworth
Mark Petrie, Glasgow
Aaron Ranasinghe, Birmingham
Sanjit Singh, Glasgow
Steven Tsui, Papworth

Apologies: Mohamed Al-Alaloul, Manchester
Nawwar Al-Attar, Glasgow
Stephen Clark, Newcastle
Andrew Fisher, Newcastle
Neil Howell, Birmingham
Gabriel Oniscu, Edinbugh
R Venkataswaran, Manchester

1. Welcome and introduction

2. Background of initiative

   Professor Peter Friend outlined RCS initiative to facilitate discussions to increase surgical research in the transplant field.

3. CTAG audit perspective

   N Banner explained 3 of the areas that the CTAG Audit Group had been working on:

   a. ISHLT definition of PGD base on inotrope score, IABP, MCSD use. Discussion around the need to have a detailed registry, prospectively collect objective donor and recipient data including haemodynamic, echo, metabolic and biochemical parameters that may predict outcomes. Difficulties with compliance could be address by CQUIN and Redcap (Vanderbilt on-line data collection tool). Plan to collect individual unit data by visiting centres to further develop this idea. **Action: S Singh**

   b. BSD to decision interval – retrospective data suggested higher donor heart use when retrieval (time of abdominal organ perfusion) delayed to 36 hrs from BSD diagnosis (fixed dilated pupils). PJF suggested benefit of delayed retrieval for kidneys as well (lower PGD). Potential concerns of delayed

retrieval on donor lung function but UK data may suggestno harm; need to confirm with John Dark. However, to demonstrate an increase of retrieval rate from 20% to 30% would require approximately 800 donors. Discussion of whether this should apply to all donors or just those with marginal cardiac function. Lots of stakeholders including abdominal teams, donor hospitals and organ donation staff. Worth developing research proposal further. **Action: R Venkat**

c. Use of OCS for selected donor/recipients: POTECT II showed non-inferiority compared with cold static preservation for standard criteria hearts. Next step is EXPAND, largely US centres, "extended" criteria equivalent to many hearts routinely used in Europe already. Option to randomise the European marginal donors to cold static preservation and OCS, end point of PGD. Alternative of UK/EU EXPAND single cohort to go beyond the US EXPAND criteria. Reservation would be high cost of device and OCS experience limited to 2 centres at present and there is a learning curve.Worth taking forwards. **Action: Diana Garcia?**

4. Research Ideas:
    a. Cardiac allograft protection study
        i. Actively lowering LDL cholesterol to pre-set target level with statins. Assess CAV with IVUS. N=266 over 3 years. Letter of invitation distributed at meeting.Replies to Harefield. **Action: ALL**

    b. Circulating donor-derived DNA (cell free) can pre-date biopsy positive rejection by up to 6 months and appears to be a potential biomarker for rejection and immunosuppression monitoring. GOSH will be initiating a biobank to prospectively collect recipient blood samples post-transplant to coincide with biopsies. 5ml sample, results in 48 hrs. PJF indicated potential interests from abdominal transplant centres. All CT Tx centres are invited for an expression of interest. To circulate protocol. **Action: M Fenton**

    c. Upregulation of endothelial nitric oxide synthase (eNOS) through nanoparticle gene transfer to reduce intimal hyperplasia and CAV. Studies with saphenous veins showed promise even with adventitial exposure for just 15 minutes. Potential use in donor organ as a flush to modify response to ischaemic reperfusion injury. GOSH will be looking for collaborators to develop animal transplant model to test this approach in the preservation fluid. **Action: M Fenton**

    d. Markers for aspiration in lung donors e.g. bile acids. Fits in well with QUOD initiative which will start collecting 60 mL of BAL from all lung donors. This will enable batch testing of collected samples and correlate with clinical outcomes of transplanted lungs. **Action: J Parmar**

    e. The use of real time imaging to aid donor organ assessment e.g. Google glasses. There is interest in using such technology but difficult to develop this into a research study from the outset. One option would be to collect a library of images and then ask clinicians which organs they would or wouldn't use, blinded to actual usage and outcomes. **Action: J Parmar**

f. The role of T3 in marginal heart donors. Need to define "marginal" criteria, dosage, time of administration power calculation and outcome measures. May overlap with (3b) and needs careful planning, perhaps with a factorialstudy design. Worth taking forwards. **Action: R Venkat**

g. Randomised trial of LVAD versus OMM. Appropriate to compare modern LVAD with modern OMM. Likely to be supported by UK heart failure community and is the sort of project that the HTA should be interested in. Worth taking forwards. **Action: M Petrie**

h. Randomised trial of elective heart transplant versus OMM. Probably worthwhile but likely to require a large number of subjects making a UK-only study not achievable. Reserve idea for now.

i. Glasgow Transplant Score. Pilot data from 20 post heart transplant patients analysed. Idea in development. Further refinement to be carried out and progress will be reported. **Action: S Singh**

j. Post-conditioning using cyclosporine for mitochondria protection. Found to be as effective as intermittent vessel occlusion in NSTEMI. May be applied to heart transplant recipients. Alternative is to consider using cyclosporin systemically in donors as pre-conditioning agent which may benefit other donor organs. Worth taking forwards. **Action: A Ranasinghe**

5. Next steps:

   a. If proposers of the above ideas would like to take these projects forward, it is suggested that they draft a brief proposal (1 or 2 sided of A4) and circulate for discussion within 1 month (i.e. by 2nd December 2015)

   b. Proposers should aim to convene a focused group to further develop their proposal within 3 months (i.e. by 2nd February 2016)

   c. The wider research meeting could be reconvened in 6 months' time for proposers to report progress

6. We are grateful to the Royal College of Surgeons of England for sponsoring this research meeting and to Professor Peter Friend for convening and facilitating.