COPE WP2: A multicentre randomised controlled trial to compare the efficacy of ex-vivo normothermic machine perfusion with static cold storage in human liver transplantation

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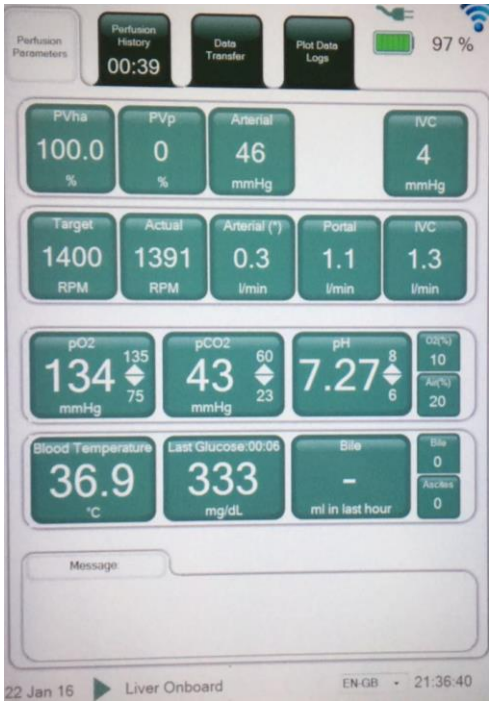
Dear [redacted]

Below are the details regarding a Serious Adverse Event that was reported on [redacted] by the research team at [redacted] and resulted in the discard of a liver enrolled in the trial entitled A Multicentre Randomised Controlled Trial to Compare the Efficacy of Ex-vivo Normothermic Machine Perfusion with Static Cold Storage in Human Liver Transplantation (Ethics ref 14/LO/0182; MHRA ref. CI/2014/0007).

On [redacted] a liver was randomised to normothermic machine perfusion by the WP2 research team in [redacted] A member of the Oxford WP2 research team was requested to attend for the retrieval in [redacted] due to a lack of staff being available and so this was provided. The donor was an 84 year old, DBD, Caucasian male in [redacted]. The retrieval proceeded uneventfully with cross clamp at 21:10.

A standard liver backtable was performed; the liver had normal anatomy, was mildly steatotic and was cannulated and connected to the machine in the standard manner. Normothermic machine perfusion was commenced at approximately 22:00.



From the start of NMP the approximate flows through the liver were as follows: hepatic artery 300ml/min; portal vein 1.1L/min; IVC 1.3L/min (image right). The pH of the circuit reached 7.3 by 45mins perfusion with lactate falling to 0.4mmol/L by 1 hour perfusion.

However, it was apparent from early in the perfusion that the machine was failing to achieve a target hepatic artery pressure of 65-80mmHg, instead only reaching approximately 45-50mmHg. This in combination with a reported hepatic artery pinch valve closure of 100% (should usually read 88-93%) suggested a possible underlying device problem to account for the failure to achieve satisfactory pressure.

In an attempt to resolve this problem the perfusion was stopped and restarted (this should reset the pinch valve calibration). The cannulae positions were also assessed but appeared satisfactory.

The problem did not resolve with these simple interventions. Despite this the liver appeared healthy and all biochemical parameters (pH, lactate, glucose) as well as bile production were satisfactory. A decision was made to transfer to Leuven to make a further assessment of

the organ. A message was sent to the transplanting surgeon [redacted] advising to wait until the liver had arrived before commencing surgery due to possible concerns about the organ.

The ambulance journey commenced and it was soon noticed that the power inverter in the ambulance was not working, so the machine was being powered only by its internal battery supply. The battery life was considered insufficient to last the entire journey to [redacted] so, once the battery had depleted to 50% it was decided that the safest action was to wait at a service station with the machine plugged in until a replacement ambulance could arrive.

Whilst waiting at the service station the user again examined the perfusion device when a further problem developed where air was noticed in the hepatic artery line (image right). Due to lack of sterile facilities this could not be investigated further at that time and the cause for it is still not known. Shortly after this the replacement ambulance arrived and the journey was completed to Leuven.

On arrival at University Hospital Leuven it transpired that the transplant surgery had commenced as the message to not commence surgery had not reached the transplanting surgeon until shortly after knife-to-skin. However, no irreversible steps had been taken during the surgery and the operation had been paused in anticipation of the liver's arrival. On assessing the organ there was no longer any air in the arterial line and the liver appeared to be perfusing homogeneously. The lactate was 0.2mmol, pH 7.31 with glucose 6.5mmol and continued bile production of 6-8ml/hr. AST levels were also monitored over a 60minute period and found to be stable at approximately 200 IU/L. However, arterial perfusion pressure remained approximately 40mmHg with the pinch valve displaying 100%. The machine was displaying arterial flow of 200-300ml/min. [redacted] used Doppler ultrasound to directly assess the arterial flow which demonstrated flow of only 50ml/min.

Due to the combination of the following factors, a decision was made to discard the liver:

- Organ was already considered marginal due to donor age (84 years old) and steatosis
- Concerns about air in arterial line
- Low arterial perfusion pressure
- Lower flows demonstrated on Doppler scan than were being displayed by the machine
- No irreversible steps had been taken in the recipient operation
- A alternative organ was available for the same recipient

The recipient was successfully transplanted with a different liver less than 24 hours later.

From a global experience of more than 150 normothermic liver perfusions using the OrganOx *metra* this is the first such incident of this type to have been reported. The OrganOx *metra* machine from [redacted] returned to the OrganOx offices shortly after this incident. Investigations revealed a mechanical fault with the hepatic artery pinch valve. The device has been returned to the manufacturing warehouse for repair according to OrganOx specifications.

Please let me know if you need any further information.

Best wishes,

[redacted]