Ex situ fibrinolytic therapy during normothermic liver perfusion before transplantation clears intravascular fibrin and is associated with minimal cholangiopathy

Christopher Watson[1, 2], Christopher Bridgeman[3], Stephen Macdonald[3], Corrina Fear[1], Lisa Swift[1], Rachael Webster[1], Lee Hope[1], Rohit Gaurav[1], Andrew Butler[1, 2]

1. The Roy Calne Transplant Unit, Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom
2. University of Cambridge Department of Surgery, Addenbrookes Hospital, Cambridge, United Kingdom
3. The Coagulation Laboratory, Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom

UNIVERSITY OF CAMBRIDGE

NHS Cambridge University Hospitals NHS Foundation Trust

INTRODUCTION

Ex situ normothermic liver perfusion (NMP) enables preservation, assessment and treatment of livers before transplantation.

We have previously shown that

- Fibrin forms within vessels in livers during cold storage (1);
- Fibrin within peribiliary vessels during NMP is associated with bile duct necrosis (2);
- Alteplase with FFP appears to stop fibrin associated bile duct necrosis (2);
- Livers release D-dimers during normothermic machine perfusion (1).

AIM

To assess the effect of fibrinolytic therapy with alteplase (recombinant tissue plasminogen activator, rTPA, a fibrinolytic drug), and fresh frozen plasma (FFP, a source of plasminogen), on:

1. the release of D-dimers from the liver during NMP
2. non-anastomotic biliary strictures (NAS)
3. transplant survival
4. post implant bleeding

METHOD

Infusions of alteplase and FFP were given to livers undergoing NMP in back-to-base mode on the OrganOx *metra* as part of 2 separate studies since 1st Feb 2018. These were compared to livers undergoing NMP which did not receive this treatment. There were a total of 200 transplants involved.

CONCLUSIONS

Treatment with alteplase plus FFP:

- is associated with greater D-dimer release during NMP, suggesting more fibrin is cleared from the vascular bed;
- minimises the incidence of biliary complications;
- is not associated with excess bleeding.

RESULTS

1. D-dimer release (figure 1)

D-dimers were measured in the perfusate after 2 hours in 188 perfused livers, of which 54 had been treated with alteplase plus FFP during perfusion; the rest were not.

Livers that received the fibrinolytic treatment had significantly higher D-dimer release (median 5782 vs 2600ng/ml, p=0.0002).

2. Cholangiopathy (NAS) (figure 2)

Of the 36 *transplanted* livers treated with alteplase + FFP, one DCD liver (5%) developed a stricture at the confluence of the hepatic duct related to cannulation technique; no other alteplase + FFP-treated DCD or DBD liver developed NAS.

Of the 164 untreated livers, 9.2% DBDs and 20.1% DCDs developed NAS within a year.

3. Transplant survival (figure 3)

Transplant survival (death or graft loss) at 1y was better for DCD livers treated with alteplase + FFP than without, but did not reach significance (100% v 89.8%, p=0.161, logrank). Similarly there was no difference in DBD livers by treatment. In the DBD group with alteplase + FFP, early graft losses were due to a HAT and biopsy complications.

4. Post implant bleeding (figure 4)

The proportion of blood replacement in terms of units of packed red cells given post reperfusion of the liver in the recipient compared to the total blood replacement was similar in both livers treated with alteplase + FFP and untreated livers, suggesting that the use of alteplase was not associated with haemorrhagic complications.

Hilar strictures.

Of the 21 NAS seen in this study, 9 (43%) predominantly affected the 1st and 2nd order ducts. We believe this is due to tying in the bile duct cannula before NMP begins, and is minimised if it is tied in after undergoing NMP for 15 minutes.

Figure 1: 2-hour D-dimer concentrations comparing livers receiving and not receiving alteplase + FFP

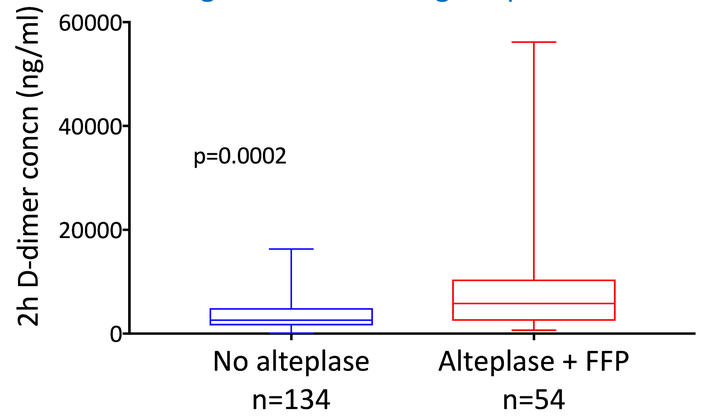


Figure 2: Proportion of livers developing cholangiopathy according to donor type and treatment.

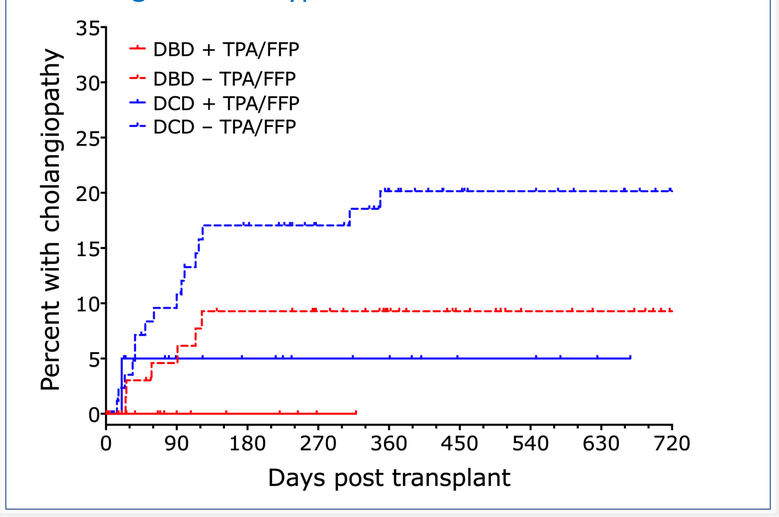


Figure 3: Transplant survival according to donor type and treatment

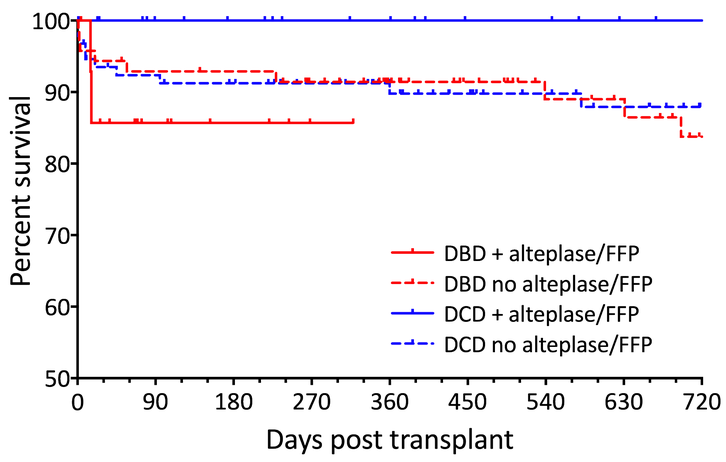
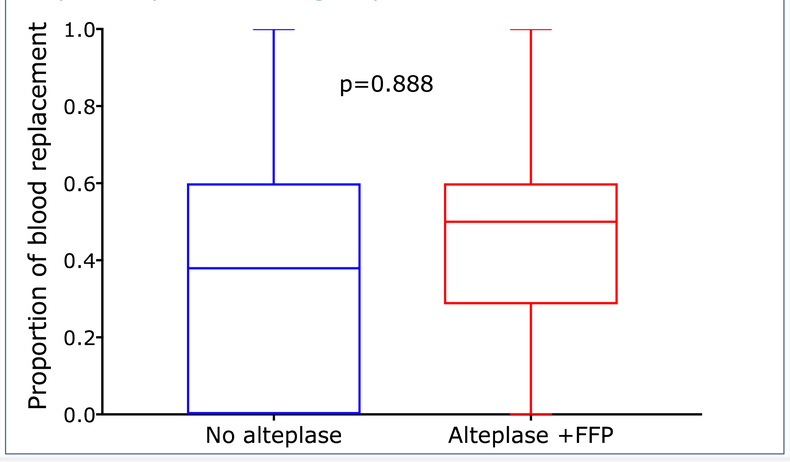


Figure 4: Proportion of blood replacement given post implant by treatment group



REFERENCES

1. Watson CJE *et al.* D-dimer release from livers during *ex situ* normothermic perfusion and after *in situ* normothermic regional perfusion: evidence for occult fibrin burden associated with adverse transplant outcomes and cholangiopathy. *Transplantation* 2023 in press

2. Watson CJE *et a*l. Peribiliary intravascular fibrin occlusions and bile duct necrosis in DCD livers during ex situ perfusion: Prevention with tissue plasminogen activator and fresh frozen plasma. *Transplantation* 2021;105:e401

ACKNOWLEDGEMENT

We would like to thank the donors and their relatives, and the recipients who took part in these studies

CONTACT INFORMATION

Chris Watson, email: cjew2@cam.ac.uk