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# An Audit of the Variety of the Use of Blood Products During Liver Transplantation in Three UK Liver Transplant Centres

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**Introduction:** Intraoperative blood and products usage during Liver Transplantation (LT) may vary between LT centres.

**Methods:** Retrospective audit of adult patients undergoing LT for chronic liver disease at three UK transplant centres (Termed A, B and C) was undertaken. Patient demographics, transplant characteristics, baseline blood testing, donor characteristics, blood and products usage and one-year survival were compared.

**Results:** With respect to baseline blood test, significantly lower fibrinogen and haemoglobin pre-operative levels were observed in centre C. Patients undergoing LT at Centre A received a significantly smaller volume of Processed Red Blood Cells (PRBCs) (Median 0mL) than Centres B or C (Median 560mL and 750mL, respectively). With respect to Fresh Frozen Plasma (FFP) use, Centre B used significantly more (median 1796mL) than Centre A (median 1000mL) and Centre C (median 0mL). Total blood products used intraoperatively were statistically different between all centres (Median 1500 mL vs 2742ms vs 1000mL respectively). One-year survival was very similar in all three centres (Centre B 95%, Centre C 93.3% and Centre A 92.6%).

**Discussion:** This audit demonstrates the varied nature of blood and products transfusion practices among the study centres but did not demonstrate the impact of the use of blood and products intraoperatively on one-year survival.

**Keywords:** liver transplantation, blood transfusion, anaesthesia

## Introduction

Liver transplant (LT) surgery remains the treatment option of choice for end-stage liver disease (ESLD). Patients undergoing LT are still at risk of suffering from massive haemorrhage, and with it the need for intraoperative transfusion of blood and blood products: fresh frozen plasma (FFP), cryoprecipitate, platelets (Pt), albumin and fibrinogen.[1] There is still not good evidence that reduced blood and products transfusion contribute to better outcomes following LT.[2–4]

Blood transfusion practices and patient blood management have changed over time. Old understanding of the cause of bleeding during LT in patients with liver disease was that it was caused by deficit of clotting factors II, VII, IX and X, low platelet count and fibrinogen level and that transfusion of FFP, cryoprecipitate and/or platelets intraoperatively can reduce the bleeding.[5]

Relatively new understanding that despite deficit of clotting factors in patient with end stage liver disease (ESLD) is that there is also deficit of pro-coagulant factors, such as antithrombin III, protein C and protein S, which keep a balance between pro and anticoagulant factors and homeostasis.[6] New understanding is that portal hypertension is the main cause of bleeding during LT and that instead of starting LT with FFP transfusion in order to correct clotting factors deficit, keeping LT patients hypovolaemic before reperfusion may more effectively reduce the bleeding and blood and products transfusion.[7–9]

Based on the authors' communication with all UK LT centres and meetings' presentations and publications, of the seven centres in the UK that perform LT, there remains great disparity with regard to intraoperative fluid management,

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blood and blood products administration and interpretation of both laboratory and point of care testing modalities. Additionally, the typical case mix of each of the UK centres varies significantly, which is likely to impact the nature of the LTs undertaken in terms of both complexity, blood loss and requirement for blood products.

This paper aims to compare the intraoperative blood and blood products usage during LT across three UK LT centres. One-year mortality published in national LT data were used as an outcome.[10]

## Materials and Methods

Retrospective case review of adult patients undergoing LT surgery at each of three chosen LT centres in the UK for indications related to chronic liver disease (CLD) was undertaken.

Patient consent to review their medical records anonymously was not required by the IRB, covering patient data confidentiality and compliance with the Declaration of Helsinki. Ethic Committee approval was waved on the basis that we retrospectively evaluated patients' data.

The audit was registered and approved at the King's College Hospital audit databases.

All organs were donated voluntarily with written informed consent, and that was conducted in accordance with the Declaration of Istanbul.

This sample population included patients undergoing either primary or re-do LT between 1st January 2017 to 31st December 2017. For ongoing centre anonymity, hospitals will be termed Centre A, Centre B and Centre C.

All patients received ongoing clinical care as directed by the responsible anaesthetist, and in accordance with local guidelines and practices.

All patients received a general anaesthetic with invasive monitoring, including an arterial line, central venous catheter (CVC), and rapid infusion line. To help guide fluid therapy and the administration of blood and blood products, clotting factors and antifibrinolytics, blood sampling was performed at induction of general anaesthesia (GA), post reperfusion and at the end of surgery. This included arterial blood gas (ABG) analysis, formal laboratory coagulation testing (Fibrinogen, platelet count (Plt), haemoglobin (Hb) and International Normalisation Ratio (INR)) in all three centres, Thromboelastography (TEG) in centres B and C, and Rotational thromboelastometry (ROTEM) in centre A. Cell salvage was used routinely in all three transplant centres. None of the centres included in the study employed veno-venous bypass. All three centres had the same haemodynamic targets and transfusion threshold.

In terms of the blood, blood products and fluids replacement centre A preferred albumin as an intraoperative colloid, centre B preferred FFP as intraoperative colloid/crystalloid, while centre C had quite flexible strategy on blood and products transfusion with intention to reduce them as much as possible.

Noradrenaline was used as the vasopressor in all three centres. All patients were recovered, extubated and received ongoing postoperative care at an intensive therapy unit (ITU).

Data were collected and analysed retrospectively through the interrogation of local patient databases and corresponding case note review as appropriate. Patient demographic data were collected, including patient age, gender, body mass index (BMI), Model for End-stage Liver Disease (MELD) Score, United Kingdom Model for End-stage Liver Disease (UKELD) Score, and baseline laboratory blood tests.

Transplant related data was collected, including donor type (Donation after Cardiac Death (DCD,) Donation after Brain Death (DBD) or Living Related donation (LRD) and graft type (whole or split livers). Additionally, intraoperative fluid therapy and blood and blood product usage were recorded, including the volume of crystalloid, colloid, PRBCs, FFP, platelets and cryoprecipitate given.

Outcomes data, 1- and 3-year mortality were collected from the Health Service (NHS) Blood transfusion (BT) Annual Report of Liver Transplantation.[10]

Patients were subdivided into those undergoing primary LT and those having re-do LT surgery. Numerical data with normal distribution are presented with arithmetic mean and standard deviation, otherwise with median and range. Normality was evaluated by mathematical and graphical methods. Categorical variables are presented with absolute and relative number expressed as percentages. A comparison was then made between the overall sample population, in addition to the aforementioned subgroups, from each participating centre. This was achieved using One-Way ANOVA with Tuckey post-hoc testing or Kruskal–Wallis with Mann–Whitney U to compare three centres by numerical variables

with or without normal distribution, respectively. The difference in frequency of categories within independent samples was evaluated by Chi-square or Fisher's exact test as appropriate. All statistical methods were considered significant for the level of confidence of 0.05. Statistical analysis was done in IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

# Results

## Patient Demographics and Recipient Data

A total of 377 patients were included in our investigation, across the three sites, with 79 patients undergoing LT at Centre A, 181 patients undergoing LT at Centre B and 117 patients having LT surgery at Centre C. They represented 50.13% of all LTs in 7 transplant Centres in the UK.

A summary of patient demographics and baseline data can be seen in Table 1. Here, it can be seen that there were differences in case load between three LT centres. A total of 334 patients underwent their first LT during the investigation period, with 70 patients undergoing first LT at Centre A (88.6% of cases), 156 patients at Centre B (86.2%), and 108 patients having their first LT at Centre C (92.3%). Remaining 41 patients underwent re-do LT surgery, with no significant differences in terms of number of patients, recipient UKELD scores, ages or baseline blood tests.

Of the baseline blood tests analysed, the baseline Haemoglobin (Hb) and fibrinogen were the only two values to have a significant difference across the three sites, with Centre C demonstrating a significantly lower baseline fibrinogen (2.14 $g.L^{-1}$) than Centre A (2.99 $g.L^{-1}$) or B (2.77 $g.L^{-1}$) and significantly lower baseline Hb than centres B and A.

## Donor Characteristics and Intraoperative Blood Product Usage

Table 2 displays the proportion of donor organs utilised by each centre (DCD and DBD donors), in addition to how many of those organs were transplanted as whole livers, and how many were split prior to transplant. There was no statistical difference between centres in terms of graft type.

Table 2 also demonstrates the median volumes of blood product used intraoperatively for these patients. Patients undergoing LT at Centre A received a significantly smaller volume of PRBCs (Median 0mL) than Centres B or

**Table 1** Baseline Recipient Characteristics for All Patients, Across Three Participating Centres

| Characteristic | Centre A | $p^a$ | Centre B | $p^b$ | Centre C | $p^c$ | $p^d$ |
|---|---|---|---|---|---|---|---|
| Number of patients | 79 | / | 181 | / | 117 | / | / |
| Age, mean ±SD | 50.89±14.61 | 0.802 | 51.41±13.26 | / | Data Not Available | / | 0.802 |
| Gender, M/F | 51/28 | 0.725 | 62/38 | / | Data Not Available | / | / |
| BMI, mean ±SD | 28.89±5.90 | 0.049 | 26.85±5.63 | 0.05 | 26.68±4.66 | 0.967 | 0.040 |
| Haemoglobin, mean ±SD | 114.7±20.95 | <0.001 | 112.52±25.12 | <0.001 | 111.19±21.48 | 0.858 | <0.001 |
| Platelets, med (Q1-Q3) | 89 (66–123) | 0.284 | 98 (66–98) | / | Data Not Available | / | / |
| INR, Med (Q1-Q3) | 1.40 (1.20–1.70) | 0.882 | 1.38 (1.22±1.78) | / | Data Not Available | / | / |
| Fibrinogen, mean ±SD | 3.01±1.10 | 0.511 | 2.82±1.36 | <0.001 | 2.13±1.04 | <0.001 | <0.001 |
| Creatinine, med (Q1-Q3) | 74 (56–99) | 0.715 | 76 (59.5–101.5) | / | Data Not Available | / | / |
| Bilirubin, med (Q1-Q3) | 54 (29–132) | 0.056 | 43 (21–90) | / | Data Not Available | / | / |
| Natrium, mean ±SD | 135.92 ± 3.58 | 0.171 | 136.72±4.61 | / | Data Not Available | / | / |
| UKELD score, mean ±SD | 55.37± 4.72 | 0.91 | 55.01±6.41 | 0.278 | 53.93±5.45 | 0.278 | 0.204 |
| MELD score, mean ±SD | 18.58± 6.43 | 0.002 | 14.57±10.14 | 0.162 | 16.24±27.02 | 0.258 | 0.003 |

**Notes**: For a statistical difference of 0.05, $p^a$:Centre A vs Centre B, $p^b$: Centre A vs Centre C, $p^c$: Centre B vs Centre C.

**Table 2** Transplantation Characteristics for All Patients

| Characteristic | Centre A | $p^a$ | Centre B | $p^b$ | Centre C | $p^c$ | $p^d$ |
|---|---|---|---|---|---|---|---|
| Donor, n | 79 | / | 181 | / | 117 | / | / |
| DBD, n(%) | 63 (79.7) | / | 137(76.1) | / | Data Not Available | / | / |
| DCD, n(%) | 14 (17.7) | / | 43(23.9) | / | Data Not Available | / | / |
| LRD, n(%) | 2 (2.5) | / | 0(0.0) | / | Data Not Available | / | / |
| Whole graft, n (%) | 75(96.2) | / | 173(95.6) | / | Data Not Available | / | / |
| Split graft, n(%) | 3(3.8) | / | 8(4.4) | / | Data Not Available | / | / |
| PRBC (mL), med (Q1-Q3) | 0(0–562.5) | <0.001 | 500 (0–1400) | 0.001 | 750 (0–1000) | 0.423 | <0.001 |
| FFP (mL), med (Q1-Q3) | 1000(0–1500) | <0.001 | 1796(1054–1796) | <0.001 | 0(0–875) | <0.001 | <0.001 |
| Platelets (mL), med (Q1-Q3) | 250(0–500) | 0.859 | 208(0–4830 | 0.034 | 0(0–250) | 0.007 | 0.02 |
| Cryoprecipitate (mL),med (Q1-Q3) | 0(0–0) | 0.106 | 0(0–424.5) | 0.101 | 0 (0–0) | <0.001 | 0.00 |
| All products (mL), med (Q1-Q3) | 1500(500–2750) | <0.001 | 2742(1641–4594) | 0.101 | 1000 (0–2250) | <0.001 | <0.001 |
| Crystalloid (mL) med (Q1-Q3) | Data Not Available | / | 100(0–1000) | / | 1000(1000–1500) | <0.001 | <0.001 |
| Colloid (mL) med (Q1-Q3) | Data Not Available | / | 1500(1000–2000) | / | 0(0–0) | <0.001 | <0.001 |
| Tx,yes n(%) | 8(10.1) | 0.273 | 25(13.8) | 0.404 | 8(6.9) | 0.64 | 0.113 |

**Notes**: For a statistical difference of 0.05, $p^a$: Centre A vs Centre B, $p^b$: Centre A vs Centre B, $p^c$: Centre B vs Centre C.
**Abbreviations**: n, number of patients; DBD, Donation after brain death; DCD, Donation after cardiac death; LRD, Living related donation; PRBC,Packed Red Blood Cells; FFP, Fresh Frozen Plasma.

C (Median 560mL and 750mL, respectively), and that patients undergoing LT at Centre C received a significantly smaller volume of platelets (Median 0mL) than those at Centres A or B (Median 250mL and 208mL respectively). With respect to FFP use, Centre B used significantly more (median 1796mL) than Centre A (median 1000mL), which used significantly more than Centre C (median 0mL).

A subgroup analysis comparing patients undergoing their first LT and re-do LT at each site showed a similar pattern of blood product use between centres.

## Frequency of Blood Product Usage

Perhaps the clearest indicator of the heterogenous nature of blood transfusion practices across LT centres of the UK can be seen in Table 3. This table shows the number and percentage of patients undergoing LT at each of the three participating centres that

**Table 3** Frequency of Blood Products Usage per Patient, by Participating Centre

| Number of Patients | Centre A | Centre B | Centre C | p |
|---|---|---|---|---|
| PRBC, n(%) | 38(48.7) | 122(67.4) | 80(68.4) | 0.008 |
| Cell Salvage, n (%) | 14(18.2) | 127(75.1) | / | <0.001 |
| FFP, n (%) | 50(64.1) | 165(91.2) | 50(42.7) | <0.001 |
| Platelets, n (%) | 41(52.6) | 95(52.5) | 45(38.5) | 0.041 |
| Cryoprecipitate, n (%) | 16(20.5) | 58(32.0) | 14(12.0) | <0.001 |
| Crystalloid, n (%) | Data Not Available | 93(51.7) | 110(94.0) | <0.001 |
| Colloid, n (%) | Data Not Available | 173(95.6) | 17(14.5) | <0.001 |

**Abbreviations**: PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma.

received particular blood products during their procedure. It can be seen that there is a significant difference in the administration of every aspect of fluid management and blood product usage across the three centres. Notably, Centre B can be seen to use cell salvage, FFP and cryoprecipitate significantly more frequently than the other participating centres. Centre A notably used PRBCs less frequently than Centres B and C, and Centre C used FFP, cryoprecipitate and colloids less frequently than Centres A or B. The use of albumin in UK LT centres is incorporated into their standard practice, however this data was not analysed.

## One-Year Patient Survival

Unadjusted one-year survival for adult elective deceased donor first LTs 1 April 2013–31 March 2017 was the highest in centre B 95%, followed by centre C 93.3% and Centre A 92.6%. Risk adjusted one-year patient survival also had the highest survival rate in centre B, 92.1%, followed by centre A, 91.3% and centre C, 88.1%.[7] Based on this outcome data, it seems that the volume of the centre has more impact on the one-year survival than the usage of blood and blood products during the LT surgery. The centre that used the most FFP had the lowest mortality.

# Discussion

The above data analysis clearly demonstrates great disparity among the three participating LT centres with regard to the use of intraoperative blood, blood products and fluid replacement. Whilst it may be possible that the patient population received by each centre during the investigation period mandated these observed differences, the high degree of widespread statistically significant results, in addition to the recurring patterns seen across patients undergoing their first LT and re-do liver transplants suggests inherent differences into the perioperative practice at each centre.

Our analysis included slightly more than 50% of patients that have undergone LT in 1 year in the UK. Analysis of nationwide transfusion practices may well demonstrate the fact that some centres may share similar transfusion practices.

Whilst this study population has been found to have comparable UKELD scores, in both the first LT and redo LT subgroups, this finding may not imply equal case complexity among these populations. The UKELD Score was initially devised and validated as a UK alternative to the MELD Score, and later adopted as an eligibility criteria for LT in the UK.[11,12] The model aims to predict survival following LT using laboratory data from patient blood tests. A higher UKELD score may therefore demonstrate more advanced liver disease, yet it may be affected by a range of non-hepatic factors. Additionally, the UKELD score does not incorporate patient comorbidities, predicted surgical complexity, surgical proficiency or other patient-related factors, which may predispose to an increased risk of perioperative blood loss. Currently, there is no scoring system, which takes these factors into account in the LT population. Indeed, these subtleties in intraoperative risk and perioperative blood loss are more likely to be encountered within a larger centre such as B, which performed proportionally to a greater number of LT than both centres A and C during the study period.[13–15] However, there is a great variability in what is considered a large volume centre. It varies between over 50 and over 67 LTs per year.[13–15] Based on data from the current literature, all three centres from our audit belong to a high-volume centre category. This and other factors such as graft quality, which were not analysed, may go some way to explain the increased blood product requirement observed in centre B.

Additionally, whilst a variety of guidance and international consensus statements have been published which aim to inform perioperative blood transfusion practices, these are not specific to the LT population.[16,17] Consequently, the fluid management and blood transfusion strategies observed in our study will have been dependent upon a combination of individual anaesthetist practices and individual centre policy and resultant heuristics. Some centres may have adopted a particular transfusion strategy or utilisation of specific blood products, such as FFP, more readily either through generational training of transplant anaesthetists, or centre consensus opinion. Whilst all centres have access to regular intraoperative laboratory testing in addition to a form of point of care viscoelastic testing such as TEG or ROTEM, the integration of these into blood transfusion practices will vary from centre to centre, and often clinician to clinician. Our audit has demonstrated less RBC transfusion in Centre A where ROTEM has been used for perioperative blood clotting monitoring and management. Centre A also has the longest history of perioperative use of ROTEM. Also, some centres and some LT surgeons may place greater emphasis on the adoption of a low CVP technique during hepatic dissection, thereby aiming to reduce consequent blood losses.[18,19] This illustrates a small fraction of the local differences each centre

will likely display regarding anaesthetic and surgical practice, which may ultimately impact both the propensity for blood loss, coagulopathy and the resultant need for the administration of blood products.

As all centres used a noradrenaline as a primary inotropic agent, the use of inotropes could not have affected the perioperative bleeding. There is evidence that the use of phenylephrine and terlipressin were associated with less intraoperative blood loss when compared with noradrenaline.[20]

Importantly, despite revealing widespread national variation in blood transfusion strategy, our data does not investigate the impact, potential benefits or potential harm incurred due to such differences in practice. Generally, the difference in one-year mortality was between three centres was below 5% and could not be used to calculate the correlation between perioperative blood and products replacement and outcomes. It must be stressed that intraoperative blood transfusion and fluid management practices during LT, may only represent part of the overall story. Although as anaesthetists, we aim to correct intraoperative coagulopathy and deliver an euvolaemic, normothermic patient to ICU for their ongoing recovery. Despite our best efforts, LT patients may need ongoing fluid resuscitation and the provision of blood and blood products. This was not included in our data analysis.

This audit has several limitations: 1) There are missing data, including some basic blood results and graft characteristics of the patient from centre C, data on crystalloids and colloids infusion from centre A and cell salvage data from centre C. Although the whole set of data would give us more accurate results and better understanding of perioperative fluid replacement strategies, even available data have shown significant difference in type of blood products replacement. 2) Although we intended to include as many parameters that could have affected blood and products replacement as possible, we still did not include the data related to recipients' comorbidities, quality of the graft, exact type and number of inotropes used (ie terlipressin and octreotide administration as an additional vasoconstrictor of portal vein was not recorded), and severity of portal hypertension that could have contributed to the peri operative bleeding. However, we monitored re-do LTs that are usually more complex, and patients bleed more, but we did not prove significantly more blood loss in that patient population.

This audit clearly demonstrates wide variation in patient blood seems that there is a variation within most LT centres, too. Future avenues of investigation should aim to both widen the study population and gather data from the entire perioperative journey of the UK LT patient. This should include not only intraoperative blood product administration but should also include the requirement for postoperative fluid resuscitation and blood product usage, in addition to relevant outcome measures including rate of postoperative complications, length of ITU and hospital stay, graft survival and quality of life. Ideally, this would be achieved via prospective data collection from all UK centres performing LT surgery. Thereby further investigating the differences identified in this audit, helping to generate a contemporary and specific clinical evidence base to inform future practice and blood transfusion policy.

## Disclosure

The authors report no conflicts of interest in this work.

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