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ORIGINAL ARTICLE

Predictors of blood transfusion requirement in elective liver resection

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Abstract

Background: Liver resection remains major surgery frequently requiring intra-operative blood transfusion. Patients are typically over cross-matched, and with blood donor numbers falling, cross-matching and transfusion policies need rationalizing.

Aim: To identify predictors of peri-operative blood transfusion.

Methods: A retrospective review of elective hepatic resections over a 4-year period was performed. Twenty-six variables including clinicopathological variables and intra-operative data were collated, together with the number of units of blood cross-matched and transfused in the immediate peri-operative period (48 h). Multivariate regression analysis was performed to identify independent predictors of blood transfusion, and a Risk Score for transfusion constructed.

Results: Five hundred and eighty-nine patients were included in the study, and were cross-matched with a median 10 units of blood. Seventeen per cent of patients received a blood transfusion; median transfusion when required was 2 units. Regression analysis identified seven factors predictive of transfusion: haemoglobin <12.5 g/dL, pre-operative biliary drainage, coronary artery disease, largest tumour >3.5 cm, cholangiocarcinoma, redo resection and extended resection (5+ segments). Patients were stratified into high or low risk of transfusion based on Risk Score with a sensitivity of 73% [receiver-operating characteristic (ROC) 0.77].

Conclusions: Patients undergoing elective liver resection are over-cross-matched. Patients can be classified into high and low risk of transfusion using a Risk Score, and cross-matched accordingly.

Keywords

blood transfusion, hepatic resection, liver tumour

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Introduction

Despite advances in surgical and anaesthetic techniques, blood transfusion is still required in 10–33% of patients undergoing elective liver resection.[1–5] The risks of transfusion are well documented and there is evidence that an allogenic blood transfusion in cancer resections has an adverse immunomodulatory effect associated with increased risk of tumour recurrence and poor prognosis.[6–15] The safety, efficacy and cost effectiveness of pre-operative erythropoetin[16–18] and autologous blood donation[19–21] as approaches to reducing allogenic blood transfusion are still being debated, and although they form part of a blood transfusion protocol in many centres their use is not widespread.

In the UK, the number of active blood donors has fallen 20% in the past 5 years, and with blood stocks consistently below optimal levels, strategic planning is required to manage available blood products.[22,23] This will assume even greater importance with the impending introduction of a test for new variant Creutzfeld Jacob Disease (nvCJD). The personal, financial and social implications of being tested for nvCJD are expected to deter many potential and existing donors.

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The purpose of the present study was to identify predictors of peri-operative blood transfusion in patients undergoing elective liver resection, and to evaluate whether surgery could safely be performed with fewer cross-matched units of packed red blood cells (PRBCs). Pre-operative identification of patients at high risk of transfusion would allow either cross-matching of additional units or consideration of further blood conservation strategies for this group.

Methods

All patients undergoing elective liver resections in a tertiary referral HPB unit since January 1993 have been prospectively maintained on an electronic database. A contemporary cohort of patients recruited between September 2004 and March 2008 were identified. Pre-operative clinicopathological data were collated, including age, comorbidities, pre-operative haemoglobin, pre-operative prothrombin time, pre-operative platelet count, previous liver surgery or tumour ablation, adjuvant or neoadjuvant chemotherapy or radiotherapy, number of tumours, size of the largest tumour and the presence of underlying hepatic steatosis or fibrosis.

Parenchymal transection was performed using the Cavi-Pulse Ultrasonic Surgical Aspirator (CUSA, Model 200T; Valley Laboratory, Boulder, CO, USA). Intermittent Pringle manoeuvre when required was with a 10-min on, 5-min off cycle. Haemostasis of the liver cut surface was achieved with either argon diathermy alone, or with the addition of haemostatic adjuncts such as Tacho-Sil (Nycomed, Copenhagen, Denmark) or Tisseel fibrin glue (Baxter Healthcare Corporation, Glendale, CA, USA). Where multiple resections were performed at the same time, the most extensive resection was considered the main procedure, and additional procedures (excluding metastatectomy and radiofrequency ablation) were listed as such. The total number of hepatic (Couinaud's) segments resected was determined by the procedure performed as stated in the Brisbane nomenclature.[24] Additional intra-operative data included operation performed, whether resection was performed open or laparoscopic, use of the Pringle manoeuvre and whether haemostatic agents were used on the cut liver surface. Histological diagnosis was corroborated with histopathology reports for each patient.

The number of units of PRBCs cross-matched for each patient, and the number of units transfused in the peri-operative period, taken as 48 h from time of surgery, was identified from the hospital's transfusion service electronic records. Threshold for transfusion was haemoglobin less than 8 g/dL, or less than 10 g/dL in patients with coronary artery disease or symptomatic anaemia. Patients were routinely cross-matched for 5 units of PRBCs from March 2007, and 10 units PRBCs prior to this.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The mean number of units cross-matched and transfused per patient was calculated and stratified by operation performed. To determine factors associated with blood transfusion, continuous variables were evaluated using the independent sample *t*-test, categorical variables using χ^2 and ordinal data using Kruskal–Wallis tests. All variables significant at $P < 0.05$ on univariate analysis were entered into a forward stepwise logistic multiple regression analysis. Significance was set at $P < 0.05$. The overall fit of the model to the data was assessed using the Hosmer–Lemeshow goodness-of-fit statistic (larger *P*-values imply better fit).

Variables remaining significant were used to construct a Risk Score for predicting the risk of peri-operative blood transfusion. The Risk Score was compared with patients' transfusion status and peri-operative blood requirement. The ability of the score to discriminate those patients requiring peri-operative blood transfusion was assessed by the area under the receiver-operating characteristic curve (ROC), where an area of 0.5 indicates no discrimination and an area of 1.0 indicates perfect discrimination.

Results

During the period of study, a total of 589 patients underwent elective liver resection, with 365 males and 224 females (male/female ratio 8:5). Median age was 64 years (range 20–91). Types of resection are outlined in Table 1. Four hundred and thirty-five (74%) patients had a resection for metastatic disease, 54 (9%) for hepatocellular carcinoma, 46 (8%) for cholangiocarcinoma, 49 (8%) for benign disease and 5 (1%) for other pathologies: biliary papillomatosis (2), spindle cell mesenchymal tumour (2) and a mucinous tumour of indeterminate origin.

A total of 4714 units PRBCs were cross-matched pre-operatively (median 10 units per patient). Median pre-operative haemoglobin was 13.6 g/dl. In the peri-operative period, 100 patients (17%) received 420 units PRBCs, with a median transfusion of 2 units. The ratio of units cross-matched to units trans-

Table 1 Transfusion rates by operation. Units transfused relates only to those patients who had a transfusion

Operation[31]	No patients	% of patients transfused	Median units transfused (range)
Metastatectomy	204	15%	2
Left lateral hepatectomy	64	13%	2
Left hemihepatectomy	36	14%	3
Left trisectionectomy	17	59%	3
Right hemihepatectomy	158	12%	2
Right trisectionectomy	47	40%	5
Segmentectomy	35	11%	2
Associated bile duct excision	23	16%	3
Caudate resection	5	0%	0
OVERALL	589	17%	2 (1–41)

fused was 11 : 1. Transfusion rate and volume varied by type of operation (see Table 1). Of the 4714 units cross-matched in our study, only 8.9% were used. The remaining 91.1% were returned to stock. It was not feasible to track subsequent usage of returned units for other patients, but the overall wastage rate of packed red cells in our hospital in the last financial quarter (2008/2009) was 1.63%.

Univariate analysis identified 11 variables predictive of peri-operative PRBC transfusion (see Table 2). Seven factors remained independently significant after logistic regression analysis: coronary artery disease, pre-operative biliary drainage, previous liver resection, pre-operative haemoglobin <12.5 g/dl, tumour size >3.5 cm, extended resection (≥5 segments) and a histological diagnosis of cholangiocarcinoma (see Table 3). The regression model showed no lack of fit to the data (Hosmer–Lemeshow 0.800), and good discrimination of patients requiring a peri-operative transfusion (ROC 0.777).

All significant variables on multivariate analysis were deemed to be of equal importance in predicting peri-operative blood transfusion on the basis of similar odds ratios. To construct a Risk Score for peri-operative blood transfusion, each variable was assigned a score of 1 point, giving a Risk Score range of 0–7. The proportion of patients requiring transfusion by Risk Score and the number of units transfused when required is shown in Table 4.

The Risk Score gives good discrimination of patients requiring a transfusion (ROC 0.77, standard error 0.03). Of patients transfused, the number of units transfused correlated significantly with Risk Score ($P < 0.001$, bivariate Spearman's rank correlation). Patients were stratified into those at low risk of transfusion (Risk Score <2) and those at high risk (Risk Score ≥2). Of the 100 patients transfused, 73% were in the high-risk group (sensitivity 73%, negative predictive value 92%). Thirty-two per cent of the 232 patients in the high-risk group were transfused (median 3 units; range 1–41 units) compared with only 7.5 % of the 375 patients in the low-risk group (median 2 units; range 1–3 units).

Table 2 Univariate analysis of factors predictive for perioperative blood transfusion

Variable	Not transfused (n = 489)	Transfused (n = 100)	p-value
Age (mean)	63	60	0.053
Sex = male	308	57	0.261
= female	181	43	
Coronary artery disease	54	20	0.014*
Respiratory disease	21	7	0.247
Peripheral vascular disease	20	4	0.967
Diabetes Mellitus	30	7	0.745
Previous tumour ablation	6	4	0.050*
Preoperative biliary drainage	15	15	<0.001*
Previous liver resection	66	22	0.030*
Neoadjuvant chemotherapy	86	76	0.591†
Underlying steatosis	220	36	0.098
Underlying fibrosis	80	23	0.111
Tumour size >3.5 cm	217	62	0.001*
Number of tumours (mean)	2.4	2.1	0.073
Bilateral resections	88	12	0.072
Haemoglobin <12.5 g/dl	107	47	<0.001*
Platelet count $<150 \times 10^9$	25	8	0.253
Prothrombin time >15 s	35	15	0.010*
Additional procedures	17	10	0.014*
Laparoscopic resection	27	0	0.016*
Use of Pringle manoeuvre	341	67	0.589
Use of haemostatic adjuncts	339	71	0.740
Histological diagnosis			
(p value compared to all other diagnoses)			
Metastatic disease	374	61	0.001††*
Hepatocellular carcimona41	41	13	0.145
Cholangiocarcinoma	24	22	<0.001*
Benign	47	2	0.012††
Other	3	2	0.169
Extent of resection			
(p value compared to minor resection)			
1–2 segments (minor)	233	37	–
3–4 segments (major)	180	25	0.629
≥5 segments (extended)	76	38	<0.001†††*

†Data only available for 477 of 589 patients.
††Metastatic and benign disease significantly predict *not* requiring blood transfusion.
†††Extended resection significantly predicts transfusion at $p < 0.001$ when compared to both minor and major resections.

Discussion

In the United Kingdom, the number of blood donors has fallen by 20% in the past 5 years, and stocks of donated blood are frequently below the optimal targets set out by the National Health Service Blood and Transplant Service (NHSBT). If trends continue, despite the current decline in demand for blood products, there will a predicted shortfall of 100 000–300 000 units by 2011/2012.[22,23]

A cross-matching policy for liver resection in our unit historically mirrored that for our liver transplantations, which was reduced from 10 to 5 units in March 2007 after an audit of transplantation blood usage. This resulted in over-cross-matching of liver resection patients, as evidenced by the low transfusion rate and high cross-match to transfusion ratio in this study. Our transfusion rate of 17%, with a median transfusion of 2 units in those patients transfused, is comparable to contemporary published results for liver resection.[24,25] The British Committee for Standards in Haematology (BCSH)[26] still advocates Friedman's recommendation in 1976[27] that the ratio of cross-matched to transfused PRBCs in surgery should be 2:1, but this is less applicable to liver

Table 3 Variables independently predictive of perioperative blood transfusion on multivariate regression analysis

Variable	p-value	Odds Ratio
Coronary artery disease	0.018	2.135
Preoperative biliary drainage	0.013	3.925
Redo resection	<0.001	4.488
Tumour size >3.5 cm	<0.001	2.596
Haemoglobin <12.5 g/dl	<0.001	3.661
Extended resection (5+ segments)	0.001	2.603
Histological diagnosis = Cholangiocarcinoma	0.012	3.097

Table 4 Transfusion rates by Risk Score. Units transfused calculated only for those patients who had transfusion

SCORE	No. of patients	No. of patients transfused	Median units transfused (range)
0	120	5 (4%)	2 (2–3)
1	237	22 (9%)	2 (1–3)
2	149	28 (18%)	3 (2–22)
3	59	25 (42%)	3 (1–41)
4	20	16 (80%)	4 (1–20)
5	4	4 (100%)	3 (2–5)

resections where despite a modest risk of transfusion the potential for substantial bleeding is high compared with other operative procedures.

The Maximal Surgical Blood Order Schedule (MSBOS) is widely used to guide use of blood components, but MSBOS policies vary between hospitals and do not take account of patient-specific factors. A number of studies have attempted to formulate more patient-specific tools for predicting blood transfusion,[28,29] but none have been readily adopted for liver resection patients. There is no clear consensus of blood transfusion predictors from the few studies in liver surgery patients.[24,25,30] We have demonstrated that the risk of peri-operative blood transfusion in elective liver resection can be predicted from seven variables.

Low pre-operative haemoglobin is the most obvious predictor for peri-operative transfusion, and has been shown in a number of other studies. Previous liver resection, however, was the strongest predictor of transfusion, and may relate to the technical difficulties of redo liver surgery.

It is well known that hilar cholangiocarcinoma resections involve more technically demanding procedures which may include lymph node dissection, caudate resection, and resection and reconstruction of hepatic inflow, increasing the likelihood of blood loss. The extent of liver resection and size of the largest tumour were predictive of peri-operative blood transfusion in both this study and other studies.[2,4] Larger lesions are generally more vascularized, and encroachment onto venous outflow causes more parenchymal congestion.

Patients requiring pre-operative biliary drainage (after endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography) will have had varying degrees of biliary obstruction and underlying liver dysfunction. Studies have shown no independent association between pre-operative bilirubin, alkaline phosphatase or alanine aminotransferase and blood transfusion requirement. The significance of pre-operative biliary drainage may reflect underlying liver dysfunction and coagulopathy. Although not significant in this study, prothrombin time has been identified as an independent predictor in other studies.[2]

Coronary artery disease can affect the patient's tolerance of anaemia, low central venous pressure anaesthesia and hypovolaemia. We acknowledge that the lower transfusion threshold for these patients may bias the association with peri-operative transfusion, but for the purpose of predicting transfusion and guiding preoperative cross-matching, it remains a valid and important variable in the model.

A similar study by Pulitano *et al.*[4] identified five predictors of peri-operative transfusion. Their Transfusion Risk Score had a sensitivity of 94% but their transfusion rate of 33% is almost double that in the present study. It is not clear how comparably this score would predict transfusion in cohorts of patients with lower transfusion rates. We advocate using the Risk Score to stratify patients into low- and high-risk groups pre-operatively. Low-risk patients should be group and saved rather than cross-matched, based on the low risk of transfusion (7.5%) and median transfusion when required of only 2 units (range 1–3 units). High-risk patients should be cross-matched 3 units, given that this was the median transfusion when required and that most blood transfusion services are able to electronically issue further blood within 5 min. Although we were not able to determine when in the 48-h peri-operative period blood was given, from experience it is most often given post-operatively. It may be that cross-matching fewer than 3 units is sufficient for patients in the high-risk group.

There is a financial advantage to reducing routine cross-matching. The cost of purchasing 1 unit packed red cells in 2007/2008 was £133.99. The cost of group and saving is £24 per sample and the cost of cross-matching is approximately £7 per unit. Based on 250 cases per annum and the 60 : 40 ratio of low-/high-risk patients observed in this study, the proposed reduction in cross-matching would save 1050 units of blood, with a cost saving of £7350 per annum. The actual cost of purchasing blood (£133.99) is only of significance when considering blood wastage. At an estimated surgical wastage of 2% of units cross-matched, reducing this policy would save 21 units per annum, with a further cost saving of £2814. This is particularly important in circumstances where unused cross-matched blood returned to stock is less likely to be reused, such as in smaller hospitals or for less common blood groups [e.g. group B Rh (D) Negative] where the blood is not held in local stock in high volume and may have to be ordered specifically for that patient.

There is also an important strategic benefit to reducing routine cross-matching of blood, the financial implications of which are

harder to discern. In the UK, blood components, products and services are processed and administered nationally by the NHSBT. Hospital Trusts purchase blood components to be held locally in their 'blood banks'. Reducing the amount of blood cross-matched, and thereby taken out of a hospital's available blood stock, allows transfusion services to operate with lower baseline blood stocks to meet local demand. From a national perspective this reduces demand for blood from NHSBT and reduces absolute wastage. Reducing demand for blood is important when national stock levels are low and will become a more pressing issue in the near future, with an anticipated sharp fall in blood donors when tests for nvCJD are inevitably introduced for blood donation.

The economic arguments for reducing pre-operative cross-matching must be weighed against patient safety. In advocating reducing cross-matching to 'group and save' for low-risk patients to 3 units for high-risk patients, the hospital's blood transfusion service must be aware of any abnormal antibodies that would either prolong cross-matching or necessitate the ordering in of compatible blood components. Our Unit is advised to send two preoperative 'group and save' samples to ensure this, a second sample being particularly important if there is a large delay between the preassessment clinic and operation date. In addition, good communication with the transfusion service and reliable and timely transport of blood from laboratory to operating theatres are essential.

In conclusion, this study has demonstrated that blood transfusion in elective liver resection can be predicted from seven variables. Cross-matching can be guided by use of a Risk Score, facilitating strategic and cost-effective use of blood. The Risk Score could also guide the use of other blood conservation strategies. Further work is required to prospectively validate the Risk Score, evaluate its transferability to other patient populations, and assess its benefit to the blood transfusion service with respect to management of blood stocks.

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Conflicts of interest

None declared

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