Mortality following blood transfusion for non-variceal upper gastrointestinal bleeding

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Abstract

Objective Blood transfusion remains an integral step in the management of acute non-variceal upper gastrointestinal bleeding (NV-UGIB), but its safety is being increasingly questioned in less severe cases. The authors aimed to measure 30-day and 2-year mortalities after blood transfusion for NV-UGIB.

Methods Cox proportional hazards models were used to estimate the association of blood transfusion with mortality while adjusting for age, Charlson comorbidity score, the complete Rockall score for acute UGIB, admission status and medication intake prior to bleeding.

Main outcome measures Death from any cause at 30 days and 2 years after NV-UGIB.

Results 1340 patients presented with NV-UGIB (808 men (60.3%), median age 67 years) of whom 564 (42.1%) were transfused. The overall mortality was 5.3% at 30 days and 26.0% at 2 years in all patients. Comparing subjects with a haemoglobin concentration greater than 10.0 g/dl who were transfused with those who were not, 30-day mortalities (95% CIs) were 11.5% (6.7 to 18.0) versus 3.6% (2.3 to 5.3), respectively, $p < 0.001$, and 2-year mortalities (95% CIs) were 40% (32 to 49) versus 20% (17 to 23), $p < 0.001$. After adjusting for age, Charlson score, Rockall score and haemoglobin, the HRs (95% CIs) for death after transfusion were 1.88 (1.00 to 3.55) ($p = 0.051$) at 30 days and 1.71 (1.28 to 2.28), ($p < 0.001$) at 2 years.

Conclusion In patients with moderately severe NV-UGIB, mortality is higher following blood transfusion. Whether this reflects selection bias, an effect of comorbidity or an effect of transfusion requires urgent prospective study.

Introduction

Blood transfusion has proven to be life-saving for nearly 100 years and remains an integral part of resuscitation for a wide range of medical and surgical

emergencies. Commonly used all over the world, more than 14 million units of blood are transfused annually in the USA.¹ Acute upper gastrointestinal bleeding (UGIB) is a major indication for blood transfusion, accounting for more than 400 000 hospital admissions and costing more than \$2 billion each year in the USA.^{2,3} The majority of cases (80–90%) are due to non-variceal lesions, mainly gastroduodenal ulcers or mucosal erosions.⁴ It is estimated that UGIB is the major complication leading to transfusion in patients with medical conditions, accounting for 13.8% of all blood transfused.⁵ The wisdom of this use is being questioned, given the falling donor numbers and the absence of clear benefit of blood transfusion in less severe cases of UGIB.^{5–7} Also, a recent meta-analysis of cohort studies has suggested that in various patient groups (intensive care unit, trauma and surgical) blood transfusion was associated with increased morbidity and mortality, prompting re-evaluation of current transfusion practices.⁸

The management of non-variceal UGIB (NV-UGIB) consists of endoscopic haemostasis, pharmacological therapy and supportive care and, in some cases, blood transfusion, arterial embolisation and/or surgical intervention.⁴ For nearly 50 years, mortality from NV-UGIB has remained high, 5.0–10.0%, despite advances in endoscopic, pharmacological and other interventions.^{4,9}

We, therefore, aimed to examine the possibility that blood transfusion might be a factor contributing to mortality in patients with NV-UGIB.

Methods

This is an observational analysis of mortality in subjects who presented with

NV-UGIB to Crosshouse Hospital in southwest Scotland and affiliated to the University of Glasgow over 6 calendar years: 1996, 1999, 2002, 2005, 2006 and 2007. Mortality data for this analysis were recorded until and including the last day of December 2009. The clinical details of all patients with UGIB have been recorded every third year until 2005 and annually since then. Cases of UGIB are identified from hospital records of patients presenting to all departments, particularly the acute surgical, medical, accident and emergency and endoscopy units. Their diagnoses and codes are based on the International Classification of Diseases (ICD-10) for bleeding upper gastrointestinal disorders. The work is part of an ongoing programme that assesses the epidemiology, aetiology and the management of peptic ulcers and their complications.^{10–13} NV-UGIB was diagnosed in patients who presented with UGIB (haematemesis or melaena)^{9–12} and in whom endoscopy showed no evidence of oesophageal or gastric varices, or portal hypertensive gastropathy. Causes of NV-UGIB included gastric or duodenal ulcers or erosions, erosive gastritis, Mallory–Weiss lesions, erosive oesophagitis, idiopathic angiodysplasias and upper gastrointestinal tract tumours and malignancies.

Patients with NV-UGIB were included in this analysis if they were adults, 18 years of age or older, and regardless of the cause of their UGIB or comorbidity. They were excluded if they had evidence of oesophageal or gastric varices, or portal hypertensive gastropathy. They were also excluded from the analysis if after endoscopy they did not require admission to hospital, as such patients form a distinct population with a good prognosis and their inclusion would bias the study: none of them received a blood transfusion.

Comorbidity was graded by the Charlson score and UGIB was defined as previously described.^{10–15} UGIB was defined as haematemesis, melaena or both. Haematemesis included the vomiting of fresh or altered (coffee-ground) blood as confirmed by clinical testing at primary care or in hospital. This definition excludes anaemia without overt UGIB and melaena due to proximal colonic lesions detected by colonoscopy or barium studies. Melaena, confirmed by clinical testing and frequently associated with rise in blood urea level, was considered to be of upper gastrointestinal origin, particularly in the presence of upper gastrointestinal endoscopic abnormalities and in the absence of colonic lesions.^{10–11} The Charlson score has been thoroughly validated by us and others as a measure of comorbidity in a whole range of conditions including UGIB.^{10–15} The complete Rockall risk scoring system for acute UGIB was also calculated and included both clinical and endoscopic findings and stigmata of recent bleeding.¹⁶ In Scotland, the Rockall score is recommended by National

Guidelines for the management of UGIB.¹⁷ It also uses endoscopic findings to predict mortality and has been validated in many countries.¹⁸ As mentioned above, patients' details, including the clinical components relevant to the various scoring systems, were collected annually and tabulated on regular basis for the 6 calendar years of the work while protecting patients' identifiable details. Before being tabulated by members of the research team, the clinical components or measurements, such as pulse rate, blood pressure, routine blood test results, and so on, had already been taken and documented by non-research staff caring for the patients. In this analysis, both the Charlson and the complete Rockall scores were all recalculated, reviewed and revised by two investigators (CMcC and TC), who standardised definitions and compilations of the relevant components, keeping inter-observer variation to a minimum.

Blood transfusion in this article refers to red blood cell transfusion that has been initiated within 24 h and completed within 3 days of acute UGIB. The decision to transfuse or not was taken by emergency room or acute medical unit staff, using their personal assessment of the patient's condition in accordance with nationally agreed guidelines.¹⁹ Death as an outcome was documented from hospital or primary care records. The causes of death within 30 days and 2 years were ascertained, reviewed and verified by a committee of clinicians who were not aware of the subject's transfusion status. All tests and treatments were in line with standard medical care and no randomisation or allocation to treatment groups took place, but patients' identities were concealed using code numbers. Hence, no ethical approval or patients' consent were sought: the work was approved and supported by the institutional Clinical Effectiveness and Governance Team of NHS Ayrshire and Arran, Scotland.

Statistical analysis

Comparisons of variables between transfused and non-transfused patients were performed using the Mann–Whitney test and Fisher's exact test as appropriate. Cumulative mortality was calculated using the Kaplan–Meier method and comparisons were made using the log rank test. HRs were calculated using Cox regression analysis with follow-up censored at either 30 days or 2 years after the bleeding episode, the end point being death from any cause. HRs were adjusted for age, Charlson score, Rockall score and admission haemoglobin (Hb) concentration, all of which were treated as continuous variables. Cox regression models were also examined, which included the following covariates in binary form: gender, smoking, alcohol and use of other drugs including low-dose aspirin, other antithrombotic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), statins, β blockers, calcium antagonists, ACE inhibitors, diuretics and digoxin. Admission status (admitted to

hospital as a result of bleeding vs bleeding after being admitted to hospital for another condition) was found not to satisfy the proportional hazards assumption and the analysis was therefore stratified by admission status, assuming common HRs for the covariates. SPSS 15.0 for Windows was used for all analyses.

Results

Of the 1776 patients who presented with UGIB, 90 were excluded from analysis because they had variceal bleeding, 341 were excluded because they were discharged immediately after endoscopic examination and 5 had incomplete survival and/or transfusion data. The remaining 1340 patients with NV-UGIB who were either admitted for further management of their bleeding or who bled after being admitted to hospital because of another comorbid condition were eligible for the analysis.

Of this study group, 564 patients (42%) received a blood transfusion. When the 341 excluded patients, mentioned above, are taken into account, the proportion of transfused patients is 33.6%. Details of patients grouped according to whether or not they were transfused are shown in table 1. As might be expected, patients who received transfusions were older and had higher comorbidity, worse prognostic scores, greater use of statins, aspirin and NSAIDs, and lower admission Hb concentrations than those who were not transfused. These factors were fully adjusted for in the multivariate analysis, shown below.

Cumulative mortality is plotted against follow-up time for transfused and non-transfused patients in

figure 1. Mortality was higher in transfused patients by a factor of 2.4 at 30 days (8.0% vs 3.4%) and 1.8 at 2 years (34.9% vs 19.2%). Table 2 shows mortality stratified by Hb concentration. The higher mortality associated with transfusion was particularly significant in those with a Hb level greater than 10 g/dl, although the small number of patients with Hb concentrations below 8.0 g/dl who were not transfused limits conclusions in this subgroup. Also, 33 patients who had Rockall scores of 0–2 and Hb greater than 10 g/dl were transfused, 5 of whom (15.2%) died within 2 years: 2 died of vascular events, 2 of liver disease and 1 died of renal failure.

Table 3 shows HRs associated with transfusion as determined by Cox regression analysis, initially unadjusted by other prognostic factors and then adjusted for factors related primarily to the severity of bleeding (Rockall score and Hb concentration) followed by adjustment for underlying major risk factors (age and Charlson comorbidity score). Results were similar whether follow-up was limited to 30 days or extended to 2 years, apart from lower precision at the shorter time interval due to the smaller number of events. Unadjusted HRs were greater than 2.0. Adjustment for Rockall score and Hb resulted in a decrease in HR, but there was little further change on adjustment for age and Charlson score, with fully adjusted ratios of 1.9 (95% CI 1.0 to 3.6) at 30 days and 1.7 (1.3 to 2.3) at 2 years. Further adjustment for gender and drug use as described in the Methods section produced no significant change in HRs, nor did adjustment for admission status when this was

Figure 1 Kaplan–Meier mortality curves for all transfused and non-transfused patients ($p < 0.001$, log rank test). Numbers at risk at 6-month intervals are shown below the x-axis.

analysed as a covariate rather than a stratification variable. It is worth noting that patients with serious comorbid conditions such as malignancy, diabetes with end-organ damage or severe renal or liver diseases will all score 3 or more on the Charlson index, and this and other scores have been taken into account in the above adjustments and as shown in table 3.

Table 4 presents the HRs for 30-day and 2-year mortalities (transfused vs non-transfused) adjusted for Rockall score, Hb, age and Charlson score, stratified by the volume transfused. The fully adjusted HR associated with transfusion increased progressively

with the volume transfused. When patients who were not transfused were excluded from the analysis, the variation in mortality with volume transfused was significant over a 30-day period ($p=0.039$) but not over 2 years ($p=0.32$). This corresponds to the fact that transfusion of five or more units was associated with a substantial increase in 30-day mortality but only a modest increase in 2-year mortality, relative to smaller transfusion volumes.

Table 5 shows the main causes of death in transfused and non-transfused patients. As mentioned in the Methods section, the end point for our analysis was death of any cause.

Table 1 Patients' details classified by their transfusion status

	All patients (n=1340)	Transfused (n=564)	Not transfused (n=776)	p Value
Gender				
Male	808 (60.3%)	323 (57.3%)	485 (62.5%)	0.55
Female	532 (39.7%)	241 (42.7%)	291 (37.5%)	
Age (years)*	67 (50–79)	73 (58–81)	61 (43–76)	<0.001
Bled in hospital				
Yes	464 (34.6%)	178 (31.6%)	286 (36.9%)	0.048
No	876 (65.4%)	386 (68.4%)	490 (63.1%)	
Charlson				
0	201 (15.0%)	53 (9.4%)	148 (19.1%)	<0.01
1–2	657 (49.1%)	266 (47.2%)	391 (50.5%)	
3+	480 (35.9%)	244 (43.3%)	236 (30.5%)	
Rockall				
0–2	518 (39.5%)	140 (25.6%)	378 (49.5%)	
3+	792 (60.5%)	407 (74.4%)	385 (50.5%)	
Haemoglobin (g/dl)				
≤8.0	233 (17.5%)	224 (39.9%)	9 (1.2%)	
8.1–10.0	262 (19.7%)	198 (35.3%)	64 (8.3%)	
>10.0	833 (62.7%)	139 (24.8%)	694 (90.5%)	
Smoking				
Yes	452 (34.4%)	170 (30.8%)	282 (37.1%)	0.019
No	861 (65.6%)	382 (69.2%)	479 (62.9%)	
Alcohol				
Yes	793 (60.1%)	318 (57.5%)	475 (62.0%)	0.11
No	526 (39.9%)	235 (42.5%)	291 (38.0%)	
Aspirin				
Yes	386 (28.9%)	198 (35.3%)	188 (24.3%)	<0.001
No	950 (71.1%)	363 (64.7%)	587 (75.7%)	
NSAIDs				
Yes	208 (15.5%)	107 (19.0%)	101 (13.0%)	0.004
No	1130 (84.5%)	457 (81.0%)	673 (87.0%)	
Statins				
Yes	244 (18.2%)	120 (21.3%)	124 (16.0%)	0.015
No	1095 (81.8%)	443 (78.7%)	652 (84.0%)	
Deaths				
Within 30 days	71 (5.3%)	45 (8.0%)	26 (3.4%)	<0.001
Within 2 years	346 (26.0%)	197 (34.9%)	149 (19.2%)	<0.001

*Median (IQR).

NSAID, non-steroidal anti-inflammatory drug.

Discussion

We have found that blood transfusion is associated with increased mortality in patients with NV-UGIB, particularly in those with baseline Hb level greater than 10 g/dl. The association between blood transfusion and increased mortality has been described in a number of other situations, including cardiac surgery, burns, trauma and in critically ill patients,^{1 8 20–23} but

our work is one of the first to support such an association in NV-UGIB. Despite adjustment, major causes of death in both groups were vascular complications, malignant conditions and respiratory ailments. These findings are in agreement with those of the UK National Audit, which demonstrated that the most common modes of death reported in patients with GI bleeding were respiratory failure, terminal malignancy,

Table 2 Mortality at 30 days and 2 years after upper gastrointestinal bleeding in transfused and non-transfused patients grouped by haemoglobin concentration

	Transfusion		No transfusion		p Value
Haemoglobin, g/dl	Died	% (95% CI)	Died	% (95% CI)	
30-day mortality					
≤8.0	19/224	8.5% (5.2 to 12.9)	0/9	0% (0 to 28)	0.37
8.1–10.0	10/198	5.1% (2.4 to 9.1)	1/64	1.6% (0.0 to 8.4)	0.23
>10.0	16/139	11.5% (6.7 to 18.0)	25/694	3.6% (2.3 to 5.3)	<0.001
2-year mortality					
≤8.0	68/224	30% (24 to 37)	2/9	22% (3 to 60)	0.52
8.1–10.0	73/198	37% (30 to 44)	10/64	16% (8 to 27)	0.002
>10.0	56/139	40% (32 to 49)	136/694	20% (17 to 23)	<0.001

Table 3 HRs for death within 30 days and 2 years after transfusion: unadjusted, adjusted for Rockall score and haemoglobin, and additionally adjusted for age and Charlson score

	30 Days		2 Years	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Unadjusted	2.43 (1.50 to 3.93)	<0.001	2.09 (1.68 to 2.58)	<0.001
Adjusted for Rockall score and haemoglobin	2.04 (1.05 to 3.99)	0.036	1.70 (1.26 to 2.29)	<0.001
Adjusted for Rockall score, haemoglobin, age and Charlson score	1.88 (1.00 to 3.55)	0.051	1.71 (1.28 to 2.28)	<0.001

Table 4 HRs for 30-day and 2-year mortalities (transfused vs non-transfused) adjusted for Rockall score, haemoglobin, age and Charlson score, stratified by the volume transfused

Volume transfused	No. of patients	30 days		2 years	
		HR (95% CI)	p Value	HR (95% CI)	p Value
1–2 units	190	1.27 (0.58 to 2.80)	0.56	1.52 (1.09 to 2.12)	0.013
3–4 units	221	1.94 (0.88 to 4.25)	0.10	1.90 (1.33 to 2.72)	<0.001
5+ units	135	3.52 (1.67 to 7.47)	0.001	2.00 (1.34 to 2.95)	0.001

Table 5 Main causes of death at 30 days and at 2 years in transfused (n=564) and non-transfused patients (n=776)

	30 days		2 years	
	Transfused	Not transfused	Transfused	Not transfused
Vascular complications	11 (2.0%)	7 (0.9%)	54 (9.6%)	56 (7.2%)
Malignant conditions	13 (2.3%)	5 (0.6%)	63 (11.2%)	30 (3.9%)
Pneumonia/respiratory failure	6 (1.1%)	11 (1.4%)	31 (5.5%)	35 (4.5%)
Liver failure	6 (1.1%)	1 (0.1%)	24 (4.3%)	18 (2.3%)
Renal failure	1 (0.2%)	0	13 (2.3%)	3 (0.4%)
Miscellaneous	8 (1.4%)	2 (0.3%)	12 (2.1%)	7 (0.9%)
Total deaths	45 (8.0%)	26 (3.4%)	197 (34.9%)	149 (19.2%)
χ^2 test*	$\chi^2=9.51$, DF=3, p=0.023		$\chi^2=14.02$, DF=5, p=0.015	

*Liver, renal and miscellaneous categories pooled for 30-day data because of small numbers.

septicaemia and cardiac failure.²⁴ In our analysis, 42% of patients were transfused, which is also similar to the 44% proportion transfused in the UK National Audit.⁷ We have included a relatively higher proportion of patients (24.8%) who were transfused despite having a Hb level greater than 10 g/dl, and it is not possible to explain this in the context of an observational analysis. The transfused group was older and had a higher use of statins and aspirin, and it is difficult to exclude the possibility that recognition of existing cardiovascular disease on admission led to some selection bias in the decision to transfuse. It is also possible that patients with advanced chronic diseases, particularly malignancy, and scoring 3 or more on the Charlson index, were more likely to get transfused even in the presence of Hb level greater than 10 g/dl and had in turn resulted in a higher mortality. However, this and other Charlson scores were taken into account, as shown in table 3. The HRs were all close to 2, and after adjustment, CIs included 1.05 and 1.00. For all of these reasons, it is difficult to exclude the possibility that, despite our best efforts, residual confounding may explain some or all of the apparent differences.

On the other hand, the recent national audit in UK has found a twofold increase in the risk of re-bleeding and a 28% rise in mortality following blood transfusion delivered within 12 h of admission, although mortality was not statistically significant, in patients with UGIB monitored over the duration of their admission.⁷ Like the UK audit, we adjusted for Hb level and Rockall score. We also focused on NV-UGIB, formally measured comorbidity using the validated Charlson index, included transfusion initiated within 24 h of acute UGIB and followed our patients for a much longer period, 2 years, while adjusting as far as possible for a wide range of known confounding factors.

We have found that the fully adjusted HR for 30-day and 2-year mortalities associated with transfusion increased progressively with the volume transfused, as shown in table 4, and that transfusion of five or more units was associated with a substantial increase in 30-day mortality but a only modest increase in 2-year mortality, relative to smaller transfusion volumes. Increased mortality could be explained by several mechanisms operating after blood transfusion, both in the short and long term and presenting acutely or in a delayed mode over days or even months. These include metabolic disorders (acidosis, electrolyte abnormalities, citrate toxicity) and non-infectious serious hazards of transfusion (acute lung injury, circulatory overload, coagulopathy, graft versus host disease, immunomodulation, alloimmunisation, complications from red cell storage and iron overload).^{1 20 25–27} Pro-inflammatory effects of transfusion and defects in stored red cells are also thought to increase ischaemic complications after blood transfusion.^{1 20} The metabolic disorders mentioned above, coagulopathy and circulatory overload

can all be relevant to our understanding of early mortality particularly following large-volume blood transfusion. Death within 2 years might be related to delayed complications of blood transfusion, for example, graft versus host disease and immunomodulation mentioned above, or might simply reflect patients' basic comorbid conditions such as malignancy or advanced chronic diseases. Although the precise mechanism behind the higher mortality following transfusion in our patients is not clear, the gradually increasing difference in survival over a 2-year period between transfused and untransfused subjects is striking and in keeping with similar findings in the other situations listed above. The danger signal from these studies is enough to warrant a large prospective study of the issue, carefully designed to minimise confounding.

While blood transfusion may be life-saving, in the light of the risks described above, a number of strategies have been proposed to reduce blood loss and limit the need for transfusion. These include the use of haemostatic agents, Hb substitutes, blood salvage techniques, reducing blood loss from diagnostic testing, using erythropoietin and lowering the level of Hb needed to justify transfusion.²⁸ A recent international consensus has recommended that blood transfusion should be administered to NV-UGIB patients with a Hb level of 70 g/l or less, while weighing the risks of adverse outcomes associated with anaemia against the potential side effects of transfusion in the particular case.²⁹

Endoscopic haemostatic techniques are also clearly of proven value in patients with NV-UGIB in mitigating the need for blood transfusion,⁹ and bleeding might possibly have been prevented in some of the 15.5–28.5% of cases who were using NSAIDs or aspirin.^{9–13} Nevertheless, despite such improvements, NV-UGIB is likely to remain a major problem in clinical practice with the continuing likelihood that transfusion will be considered in many cases. There is a pressing need for a definitive study of the mortality solely attributable to transfusion, in various emergency settings, free of the uncertainties inherent in observational studies. In the meantime, the hazard associated with transfusion, despite possible confounding, serves as a useful prognostic indicator of shortened survival.

In conclusion, in patients with NV-UGIB, mortality is higher following blood transfusion. The need for such intervention should be carefully weighed in every case, and alternative measures should be considered when at all possible. Unless proven otherwise in prospective randomised trials, we consider that the threshold for transfusion for patients with UGIB should be raised: in particular, those with low-risk bleeding (Rockall less than 3 and Hb greater than 10 g/dl) should not be transfused during the first 24 h of presentation.

Contributors AST planned the objectives and the strategies of the work and wrote the manuscript.

What is already known on this subject

- ▶ Blood transfusion is integral to the management of severe non-variceal upper gastrointestinal bleeding (NV-UGIB).
- ▶ The wisdom and safety of blood transfusion are being questioned in less severe cases of NV-UGIB.
- ▶ Recent meta-analysis in intensive care unit, trauma and surgical patients has suggested that blood transfusion is associated with increased morbidity and mortality, prompting re-evaluation of current transfusion practices.
- ▶ Mortality following blood transfusion for NV-UGIB remains unclear.

What this study adds

- ▶ In patients with moderately severe NV-UGIB, mortality is higher following blood transfusion.
- ▶ This mortality remained higher in transfused patients even after adjustment for age, Charlson comorbidity score, the complete Rockall score and haemoglobin.

How might it impact on clinical practice in the foreseeable future

The need for transfusion in NV-UGIB should be carefully weighed in every case, and alternative measures should be considered when at all possible, particularly in less severe cases, for example, when the haemoglobin level is greater than 10.0 g/dl.

CMcC and TC recorded the clinical details and obtained the mortality data. WJA carried out the statistical analysis. AST, CMcC, AAS and CGM were all involved in the endoscopic assessments and management of bleeders. All authors have contributed to the drafting process and have seen and approved the final version of the report.

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Competing interests None.

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