Recurrent bleeding in acute upper gastrointestinal hemorrhage: transfusion confusion

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ABSTRACT

Objective: Acute upper gastrointestinal (UGI) hemorrhage is a common, often serious condition encountered in the emergency department (ED). Previous research has suggested that transfusion of blood products may interfere with the hypercoagulable state induced by significant blood loss. Our objective was to determine whether the frequency of rebleeding is higher in patients with UGI bleeding who have received early blood transfusion.

Methods: The study was a retrospective chart review of patients admitted to hospital through the ED with a diagnosis of UGI hemorrhage. Inclusion criteria limited analysis to patients presenting with hematemesis, melena, or bloody nasogastric aspirate, in whom a UGI lesion was confirmed endoscopically during admission.

Results: A total of 214 charts were analyzed. Baseline demographic characteristics were similar in transfused and non-transfused patients. Presenting hemoglobin level was lower in the transfused group (86.5 v. 119.2 g/L, $p < 0.001$). Recurrent bleeding occurred in 99 (46%) patients and was more common in transfused patients (67 [66%] v. 33 [29%], $p < 0.001$). Logistic regression analysis revealed that transfusion and presenting hemoglobin level were the only variables with a statistically significant independent association with bleeding recurrence ($p < 0.001$ and $p < 0.05$ respectively).

Conclusions: Our results support previous research suggesting that transfused UGI bleed patients have a higher rate of rebleeding. However, because of the retrospective design, causality cannot be inferred.

RÉSUMÉ

Objectifs : L'hémorragie digestive aiguë haute est une atteinte courante, souvent grave rencontrée à l'urgence. Des recherches antérieures ont soulevé la possibilité que la transfusion de produits sanguins peut affecter l'état d'hypercoagulabilité provoqué par une déperdition sanguine importante. Notre objectif était de déterminer si la fréquence de récidives hémorragiques était plus élevée chez les victimes d'hémorragie digestive haute ayant reçu une transfusion sanguine tôt dans leur traitement.

Méthodes : Il s'agissait d'une étude rétrospective de dossiers de patients hospitalisés par le biais du département d'urgence avec un diagnostic d'hémorragie digestive haute. Les critères d'inclusion restreignaient l'analyse aux cas présentant les symptômes d'hématémèse, de méléna, ou de présence de sang dans l'aspiration naso-gastrique chez qui une lésion digestive haute avait été confirmée au moyen d'une endoscopie au moment de l'hospitalisation.

Résultats : Au total, 214 dossiers furent analysés. Les caractéristiques démographiques de base étaient semblables chez les patients transfusés et non transfusés. Le taux d'hémoglobine initial était plus bas chez les patients transfusés (86,5 v 119,2 g/L, $p < 0,001$). Les récidives hémorragiques se manifestèrent chez 99 patients (46 %) et étaient plus fréquentes chez les patients transfusés (67 [66 %] v 33 [29 %], $p < 0,001$). L'analyse de régression logistique révéla que la transfusion et le taux d'hémoglobine initial étaient les seules variables présentant une association indépendante statis-

tiquement significative avec les récidives hémorragiques ($p < 0{,}001$ et $p < 0{,}05$ respectivement).

Conclusions : Nos résultats corroborent les résultats des recherches antérieures selon lesquels les victimes d'hémorragie digestive haute qui reçoivent une transfusion présentent un taux de ré-cidive hémorragique plus élevé. Cependant, en raison de la nature rétrospective de l'étude, on ne peut conclure sur la causalité.

Key words: upper gastrointestinal hemorrhage, transfusions, blood products (complications)

Introduction

Upper gastrointestinal (UGI) hemorrhage is commonly encountered in the emergency department (ED). Published mortality rates for this condition range from 2% to 14%,[1–5] and persistent or recurrent bleeding while in hospital is the most important predictor of adverse outcome.[4] Recurrent bleeding occurs in 11% to 30% of UGI bleed patients and is associated with a mortality rate of approximately 30%.[1,2,4,6,7]

Blood product administration remains an important component of emergency management, and up to 64% of patients with UGI hemorrhage receive a blood transfusion.[1] However, no studies have evaluated the effects of transfusion on patient outcomes.

Previous studies have suggested that blood transfusion may interfere with a physiologic hypercoagulable state, thereby increasing the risk of recurrent hemorrhage.[8–10] These reports are significant, given the association between bleeding recurrence and poor outcome. Our purpose was to determine whether early transfusion affects the frequency of rebleeding in UGI bleed patients

Methods

Design and setting

We conducted a retrospective chart review of patients admitted to hospital through the ED with a diagnosis of UGI hemorrhage. The setting was a tertiary-care, university-affiliated hospital with an annual ED census of 50 000. The study protocol was approved by the hospital's institutional review board.

Patients

Patients admitted to hospital through the ED with a primary diagnosis of UGI hemorrhage (hematemesis, melena, or bloody nasogastric aspirate) were considered for inclusion. We identified consecutive cases regressively, starting with the most recent admission available. Patients were excluded if the bleeding had been found to originate from a lower gastrointestinal (GI) source, if endoscopy had not been performed, or if the chart lacked adequate documentation (e.g., missing lab values).

Definitions

Bleeding recurrence was defined as a separate episode of hematemesis or melena, or nasogastric evidence of new bleeding, occurring during admission and within 7 days of initial presentation, as witnessed by hospital staff. Early transfusion was defined as the administration of whole blood or packed erythrocytes within 24 hours of ED presentation. Patients were categorized as "rebleed with transfusion" only if they had received a transfusion before rebleeding. Hematemesis was defined as the vomiting of fresh or old blood, including "coffee grounds." Melena was defined as the passage of black or tarry stools. Shock was defined as systolic blood pressure less than 100 mm Hg *and* heart rate greater than 100 bpm.[7]

Data collection

Data were collected on standardized data abstraction forms. The reviewer (J.L.G.) was not blinded to study group or outcome. A variety of demographic and medical characteristics were recorded for each patient, along with ED presentation data (Table 1). variables. Early transfusion, if it occurred, and endoscopic diagnosis were also recorded. Outcome measures were recurrent bleeding, death, emergency surgery, hospital length of stay, and admission to and length of stay in the intensive care unit (ICU).

Statistical methods

The sample size estimate was based on an alpha level of 0.05, a beta level of 0.05, and an expected rate of recurrent bleeding of 11%.[1] We calculated that, to detect a 50% relative difference in bleeding recurrence rate, we needed 520 cases. We planned an interim analysis after a minimum of 200 charts had been examined. If rebleeding rates had achieved statistical difference ($\alpha < 0.05$) at that point, the study would be terminated.

We compared patients who had received transfusions with those who had not. The statistical significance of differences in categorical outcome data were analyzed with the chi-squared test, whereas differences in continuous variables were analyzed with Student's *t*-test. Variables that differed significantly between groups and potential confounding variables were analyzed by logistic regres-

sion to determine whether they were independently associated with the primary outcome. The following covariates were included in the analysis: blood pressure, erythrocyte count, presenting hemoglobin and hematocrit, presenting international normalized ratio (INR), shock, acetylsalicylic acid or NSAID use, anticoagulant use, coagulopathy and endoscopic finding. The dependent variables were bleeding recurrence, death, emergency surgery, hospital length of stay, admission to ICU and ICU length of stay. Statistical analysis was performed with SPSS version 7.5 (SPSS Inc., Chicago).

Results

The interim analysis showed a statistically significant difference in the rate of recurrent bleeding between groups. This fulfilled the *a priori* stopping rules, and the study was termi-

nated early, with data from 214 charts. At termination, 538 charts had been reviewed. Of these, 109 were excluded because the bleeding had a lower GI source, and 134 were excluded because no endoscopy had been performed or because critical data elements were missing. The study sample therefore consisted of 214 charts, representing 102 transfused (48%) and 112 (52%) non-transfused patients. The charts spanned the period May 1998 to July 1994.

There were no significant differences between the groups in age, sex, coagulopathy, comorbidity, or use of NSAIDs, anticoagulants, or antiplatelet agents (Table 1); however, the proportion of patients in shock was significantly higher in the transfused group, and presenting systolic blood pressure, erythrocyte count, hemoglobin and hematocrit were significantly lower in the transfused group (Table 1).

Most of the UGI bleeding (127 of 214 cases, 59%) was due to peptic ulcer disease (PUD). The prevalence of PUD was greater among transfused patients, whereas the prevalence of esophagitis was greater among non-transfused patients (Table 2).

Bleeding recurred in 99 patients (46%). The determination of bleeding recurrence was a critical outcome variable; therefore, to assess the reliability of this evaluation, two abstracters (J.L.G. and J.D.) independently reviewed the first 40 charts, and they concurred on the presence or absence of rebleeding in every case. A significantly greater proportion of transfused patients experienced rebleeding (Fig. 1). Most rebleeding occurred on the first day of admission (Fig. 2).

Although there were some substantial numeric differences in rebleeding in relation to the endoscopic diagnoses (Table 3), none of them were statistically significant within the context of this study.

In most respects, the outcome of transfused patients was significantly worse than that of non-transfused patients (Table 4).

Logistic regression revealed that early transfusion and initial hemoglobin level were the only variables independently associated with bleeding recurrence ($p < 0.001$ and $p < 0.05$, respectively). Early transfusion was also associated with ICU admission ($p < 0.001$) and length of ICU stay ($p < 0.001$). No other significant associations were found.

Table 1. Presenting characteristics of patients

Characteristic	Transfused (n = 102)	Nontransfused (n = 112)	p
Demographic characteristics			
Mean age, yr (and SD)	67.1 (3.0)	64.3 (3.3)	0.21
Sex, no. (and %)			
Male	64 (62.7)	75 (67.0)	0.43
Female	39 (38.2)	37 (33.0)	0.43
Medical characteristics			
NSAID* use, no. (and %)	48 (47.0)	43 (38.4)	0.18
Anticoagulant use, no. (and %)	9 (8.8)	4 (3.6)	0.11
Coagulopathy, no. (and %)	2 (2.0)	1 (0.9)	0.51
Comorbid illness, no. (and %)	66 (64.7)	59 (52.7)	0.08
Presence of shock, no. (and %)	7 (6.9)	1 (0.9)	0.02
Vital signs			
Heart rate, beats/min (mean and 95% CI)	95.9 (92.0–99.8)	91.5 (88.2–94.8)	0.08
Systolic BP, mm Hg (mean and 95% CI)	119.5 (114.3–124.7)	132.6 (128.3–136.9)	<0.001
Laboratory			
Erythrocyte count, × 10¹²/L (mean and 95% CI)	3.0 (2.9–3.2)	4.0 (3.9–4.1)	<0.001
Platelet count, × 10⁹/L (mean and 95% CI)	251.2 (228.9–273.6)	259.0 (235.7–282.3)	0.63
Hemoglobin, g/L (mean and 95% CI)	86.5 (82.3–90.7)	119.2 (114.9–123.5)	<0.001
Hematocrit (mean and 95% CI)	0.30 (0.3–0.3)	0.40 (0.2–0.4)	<0.001
PT, s (mean and 95% CI)	14.8 (13.6–16.0)	13.6 (12.8–14.4)	0.09
PTT, s (mean and 95% CI)	28.9 (21.8–36.0)	25.7 (24.4–27.0)	0.36
INR (mean and 95% CI)	2.0 (1.1–2.9)	1.4 (0.9–1.9)	0.25

* Includes acetylsalicylic acid. SD = standard deviation; NSAID = nonsteroidal anti-inflammatory drug; CI = confidence interval; BP = blood pressure; PT = prothrombin time; PTT = partial thromboplastin time; INR = international normalized ratio.
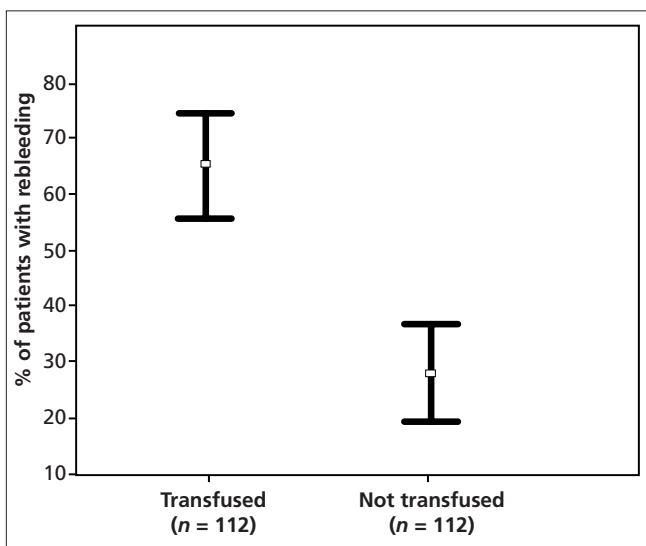
Discussion

Bleeding recurrence is considered one of the most important risk factors for death from UGI hemorrhage. In a prospective longitudinal study of patients admitted to hospital for UGI bleeding, Zimmerman and associates[4] found that persistent or recurrent bleeding was the strongest predictive factor for adverse outcome. Both Rockall and coworkers[6] and Macleod and Mills[7] found that the mortality rate among those with rebleeding was much higher (at least 30%) than among all study subjects or those without rebleeding (less than 15%). Mueller and colleagues[3] reported similar observations. Because of its demonstrated association with poorer prognosis, bleeding recurrence in UGI hemorrhage is therefore a significant complication, and identifying ways to minimize rebleeding should improve outcomes.

Previous studies have indicated that blood transfusions

may interfere with a physiologic hypercoagulable state induced by significant blood loss.[8–10] In a study investigating clotting and fibrinolytic markers in patients with UGI bleeding, Henriksson and coworkers[11] found that blood transfusion adversely affected enhanced coagulation.[11] In an experimental animal study, Henriksson and associates[10] noted that the acute loss of 20% of blood volume resulted in a significantly shortened coagulation time, but when such blood loss was followed by transfusion, coagulation time and platelet plug formation time were significantly longer than in non-transfused controls. Blair and colleagues[8] found that, in UGI bleed patients who had received transfusions, clotting times were significantly longer 24 hours after initial presentation. In addition, the proportion of patients experiencing recurrent bleeding before hospital discharge was significantly greater for the transfused group. Mueller and colleagues[3] concluded that the transfusion of more than 4 units of blood in the first 48 hours was a significant predictor of both further hemorrhage and eventual death.[3]

Our results support the concept that UGI bleed patients who receive transfusions have a higher rate of bleeding recurrence. These findings, interpreted in conjunction with the evidence from previous studies, suggest that blood transfusions may play an aggravating role in recurrent bleeding from UGI hemorrhage.

In this study, the patients who eventually received early transfusion were less stable on presentation to the ED (Table 1). Several outcome measures also indicated that the severity of illness was greater in this group (Table 4). It

Table 2. Endoscopic diagnosis by treatment group

| | No. (and %) of patients | | |
Endoscopic diagnosis	Transfused (n = 102)	Non-transfused (n = 112)	p
Peptic ulcer disease	68 (66.7)	59 (52.7)	0.04
Esophageal varices	11 (10.8)	5 (4.5)	0.08
Gastritis	10 (9.8)	16 (14.3)	0.32
Duodenitis	5 (4.9)	7 (6.2)	0.67
Mallory–Weiss tear	4 (3.9)	5 (4.5)	0.84
Esophagitis	3 (2.9)	17 (15.2)	<0.01
Gastric carcinoma	0 (0)	2 (1.8)	0.18

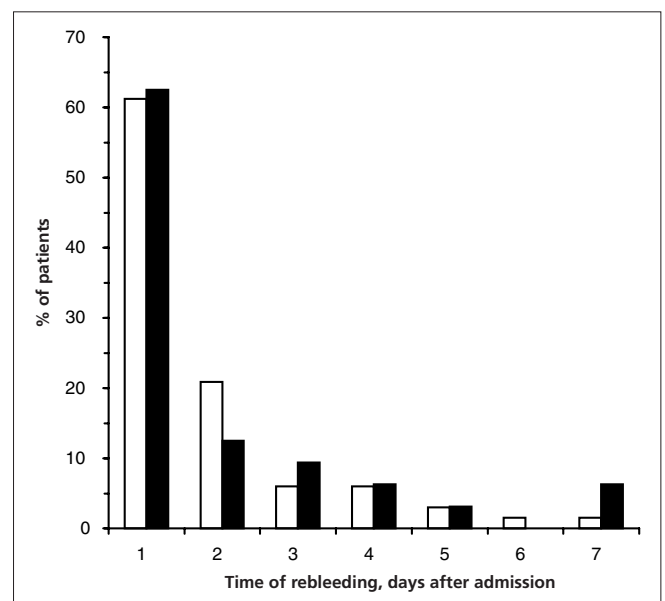

Fig. 1. Mean percentage of patients with upper gastrointestinal hemorrhage who experienced rebleeding within 7 days after admission. The difference was statistically significant (p < 0.001). Error bars represent 95% confidence intervals.

Fig. 2. Distribution of rebleeding in relation to time after admission; ☐ = transfused (n = 67), ■ = not transfused (n = 32).

is possible that these patients were inherently more likely to rebleed because of the severity of the pathology leading to the initial hemorrhage. Mueller and colleagues[3] concluded that shock was the best predictor of rebleeding. Corley and associates[2] found that initial blood pressure and a hematocrit less than 30% were independently associated with rebleeding, but we found that hemoglobin was the only presenting variable independently associated with bleeding recurrence; a low hemoglobin level in and of itself should not cause rebleeding.

The frequency of PUD and esophagitis was significantly greater in the transfused group. This finding is significant, given that certain causes of UGI hemorrhage, specifically PUD and esophageal varices, are associated with higher risk of bleeding recurrence.[7] However, Zimmerman and associates[4] reported that specific causes of UGI hemorrhage were unrelated to mortality rate,[4] and we also found no significant association between endoscopic diagnosis and rebleeding.

Limitations and future directions

The overall rate of rebleeding in this study was 46%, which was higher than previously reported rates.[1,2,4] Variation between studies in the rates of bleeding recurrence is probably due, at least in part, to differences in definitions. We defined bleeding recurrence as hematemesis, melena, or nasogastric evidence of fresh blood occurring after but within 7 days of admission. This interval should have been

adequate to identify all cases of recurrent bleeding, given that 94% of such cases occur in the first 96 hours.[12] However, with this definition there is a risk that a single prolonged bleeding episode will be classified as two separate events, which might explain the higher rate of rebleeding we obtained. Mueller and colleagues[3] identified the dilemma of distinguishing recurrent bleeding from further bleeding and noted that the distinction is sometimes impossible. Zimmerman and associates[4] identified "persistent *or* recurrent bleeding" [authors' emphasis] as the strongest factor associated with adverse prognosis factor in UGI hemorrhage. Given that we used a predetermined, objective definition and applied it equally to both study groups, the definition probably did not influence the differences we observed. In addition, our clinical definition of bleeding recurrence was similar to those used in previous studies yielding similar results.[3,5,6] It is also possible that in some patients rebleeding occurred *before* they received a transfusion but without any visible evidence of the bleeding; we had no way to determine whether this occurred.

This study was terminated at 214 patients, because an *a priori* interim analysis revealed a significant difference in the primary outcome measure (bleeding recurrence). Given that our primary endpoint was rate of rebleeding, it is possible that a larger sample size might have identified other dependent variables. However, even if such variables had been significant, their strength of association would have been weak and their contribution probably minor (because the larger the sample size required to demonstrate a statistically significant impact, the less important the true clinical result).

Conclusions and future directions

The retrospective design of this study prevents any conclusion regarding the role of blood transfusion as an causative factor in the recurrence of UGI bleeding. Further analysis of coagulation profiles before and after transfusion would provide additional insight into possible suppression of a hypercoagulable state. This retrospective study has identi-

Table 3. Rebleeding according to endoscopic diagnosis

	No. (and %) of patients		
Endoscopic diagnosis	With rebleeding (n = 99)	Without rebleeding (n = 115)	p
Peptic ulcer disease	63 (64)	64 (56)	0.24
Esophageal varices	11 (11)	5 (4)	0.06
Gastritis	8 (8)	18 (16)	0.09
Duodenitis	4 (4)	8 (7)	0.36
Mallory–Weiss tear	4 (4)	5 (4)	0.91
Esophagitis	6 (6)	14 (12)	0.13
Gastric carcinoma	0 (0)	2 (2)	0.19

Table 4. Comparison of outcome variables*

Outcome	Transfused (n = 102)	Nontransfused (n = 112)	p
Death, % of patients	3.9 (0.1-7.7)	0.0 NA	<0.05
Emergency surgery, % of patients	4.9 (0.6-9.2)	0.0 NA	<0.05
Length of hospital stay, d	8.3 (7.1-9.5)	7.9 (6.2-9.6)	0.56
ICU admission, % of patients	49.0 (39.1-58.9)	10.7 (4.9-16.5)	<0.001
Length of ICU stay, d	1.8 (0.6-3.0)	0.3 (0.1-0.5)	<0.001

NA = not applicable; ICU = intensive care unit.
* All values are presented as point estimates with 95% CIs in parentheses.

fied an association between transfusion and rebleeding. Prospective studies are required to determine possible causality and to better define the impact on outcome in these patients.

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