Evaluation of the impact of hemotransfusion on hospitalization length and complications in patients with non-variceal upper gastrointestinal bleeding

Avaliação do impacto da hemotransfusão no tempo de internamento e complicações em pacientes com hemorragia digestiva não varicosa

DOI:10.34119/bjhrv6n6-109

Recebimento dos originais: 13/10/2023
Aceitação para publicação: 15/11/2023

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ABSTRACT

Background: Upper gastrointestinal bleeding (UGB) is a common emergency associated with high morbidity and mortality. It can be caused by various factors, including peptic ulcers and vascular lesions. The decision to perform blood transfusion in stable UGB patients is still controversial, with more restrictive strategies showing better outcomes. Methods: A retrospective cohort study reviewed 1433 medical records of non-variceal UGB patients in a Brazilian tertiary care setting. Patients were divided into groups based on whether they received blood transfusion or not. Patient characteristics, laboratory values, procedures, and outcomes were analyzed. Logistic and linear regression models were used to assess the association of blood transfusion with complications and hospital stay. Results: Blood transfusion was associated with increased hospitalization length ($p<0.001$), higher rebleeding rates ($p<0.001$), and greater clinical severity. However, no association with worse renal outcomes was observed ($p=0.203$). Adjusting for clinical severity (Glasgow-Blatchford score) reduced the significance of the association with hospitalization length. Conclusion: Blood transfusion in stable UGB patients may serve as a marker of severity, associated with longer hospital stay and increased

rebleeding rates. It does not appear to have a direct causal relationship with worse renal outcomes. The study suggests that clinical severity may play a pivotal role in outcomes, as indicated by the association with Glasgow-Blatchford score.

Keywords: upper gastrointestinal bleeding, blood transfusion, clinical severity, rebleeding, hospitalization length.

RESUMO

Antecedentes: o sangramento gastrintestinal superior (UGB) é uma emergência comum associada a alta morbidade e mortalidade. Pode ser causada por vários fatores, incluindo úlceras pépticas e lesões vasculares. A decisão de realizar transfusão de sangue em pacientes estáveis com UGB ainda é controversa, com estratégias mais restritivas mostrando melhores resultados. Métodos: Um estudo de coorte retrospectivo revisou 1433 registros médicos de pacientes não-varicais com UGB em um ambiente de atendimento terciário brasileiro. Os doentes foram divididos em grupos com base no fato de receberem ou não transfusão de sangue. Foram analisadas as características dos doentes, os valores laboratoriais, os procedimentos e os resultados. Modelos de regressão logística e linear foram utilizados para avaliar a associação da transfusão sanguínea com complicações e internação hospitalar. Resultados: A transfusão de sangue foi associada ao aumento da duração da hospitalização ($p<0,001$), maiores taxas de ressangramento ($p<0,001$) e maior gravidade clínica. No entanto, não foi observada associação com resultados renais piores ($p=0,203$). O ajuste da gravidade clínica (pontuação de Glasgow-Blatchford) reduziu o significado da associação com a duração da hospitalização. Conclusão: A transfusão de sangue em pacientes estáveis com UGB pode servir como um marcador de gravidade, associada a maior permanência hospitalar e aumento das taxas de ressangramento. Não parece ter uma relação causal direta com resultados renais piores. O estudo sugere que a gravidade clínica pode desempenhar um papel fundamental nos resultados, conforme indicado pela associação com a pontuação Glasgow-Blatchford.

Palavras-chave: sangramento gastrintestinal superior, transfusão sanguínea, gravidade clínica, ressangramento, duração da hospitalização.

1 INTRODUCTION

Upper gastrointestinal bleeding (UGB) represents up to 80% of upper gastrointestinal hemorrhages (1), and it is a common emergency associated with high morbidity and mortality (2), responsible for more than 400,000 hospitalizations per year in the US with 30-day mortality over 11% (3) (4).

It can be caused by peptic ulcers, Mallory-Weiss syndrome, erosive gastritis or duodenitis (7-28%), and vascular lesions, such as angiodysplasia and Dieulafoy's lesion. Peptic ulcers are the most common cause of non-variceal UGB (25-59%), and their mortality remains between 5-10% (5).

The treatment includes hemodynamic resuscitation, the use of proton pump inhibitors, and in some cases, blood transfusion aiming to recover target organs perfusion and allow tissue perfusion (6). However, blood transfusion is associated with a higher risk of adverse events

such as acute pulmonary edema, acute kidney injury, bacterial infections, and allergic reactions (2) (6). Therefore, the decision to transfuse should be individualized for each patient (6).

For hemodynamically unstable patients, transfusion will be necessary and indicated in most cases (7). But for stable patients, the hemoglobin thresholds for which transfusion is indicated are still controversial. In the past, a hemoglobin threshold of 9 to 10g/dL was used to indicate transfusion (6). Currently, a more restrictive strategy has better results and a lower rate of complications.

This study compared hospitalization length and complications (in-hospital rebleeding and acute kidney injury) in patients admitted due to non-variceal UGB based on the strategy adopted for their treatment (hemotransfusion depending on their hemoglobin level versus non-hemotransfusion).

2 METHODS

A total of 1433 medical records of patients hospitalized due to non-variceal UGB in a tertiary care setting (Hospital Universitário Cajuru; Pontifícia Universidade Católica do Paraná; Brazil), from January 2013 to December 2018, were reviewed in this retrospective cohort study. Patients under 18 years old, and admissions not related to non-variceal UGB and pregnancy were excluded.

Data related to patient`s characteristics (age, gender, race, symptoms of UGB such as hematemesis and/or melena, antiaggregants use and comorbidities, systolic blood pressure, and heart rate at the hospital arrival), laboratory (hemoglobin, hematocrit, platelets count, INR, creatinine and urea at the hospital-arrival and the higher value during hospitalization), procedures done (nasogastric tube use and blood transfusion), esophagogastroduodenoscopy (cause of non-variceal UGB) and hospitalization (hospitalization leght in days and intensive care unit stay) were collected. For each patient, the Glasgow-Blatchford score was calculated. CKD-EPI and AKIN scales were used to estimate renal function and progression for renal dysfunction, respectively.

Patients underwent esophagogastroduodenoscopy (EGD) up to 24 hours after admission since their hemodynamical status was stable. In hemodynamical unstable patients, EGD was performed after stability. A second-look EGD was ordered for patients who rebleed (suspected by hemoglobin level decrease above 2g/dL, lack of increase in hemoglobin levels despite blood transfusion and/or presence of hematemesis or melena).

Patients were divided into 2 groups: (1) Patients who received blood transfusion (group BT); (2) Patients who did not receive blood transfusion (group NBT). Data related to the number of packed red cells transfused during hospitalization were collected for group 1.

This study was reviewed and approved by the local ethics committee (approval number 10607419.0.0000.0020).

2.1 STATISTICAL ANALYSIS

Quantitative variables were described by mean, standard deviation, minimum, and maximum. For categorical variables, frequency and percentage were presented. The association between categorical variables whether or not a blood transfusion was performed was analyzed using Fisher's exact test. The quantitative variables that showed normal distribution in the Komogorov-Smirnov test were compared between the groups that underwent and did not receive blood transfusions using Student's t for independent samples. Quantitative variables that did not present normal distribution were compared between groups using the nonparametric Mann-Whitney test.

The variables time of onset of symptoms and hospitalization length were submitted to logarithmic transformation given the non-normal distribution, which after became normal. Logarithmic versions of both variables were used in the analyses, although the descriptive results referred to direct values of time

Single and multiple binary logistic regression models were used to evaluate the Odds Ratio (OR) of blood transfusion in the development of complications individually and adjusted for time of onset of symptoms, SBP, initial CKD-EPI, and Glasgow blat. The quality of the model fitting was evaluated using the Hosmer-Lemeshow test, and their statistical significance was evaluated using the Wald test. Single and multiple univariate linear regression models were used to assess the explanatory potential of blood transfusion individually at a length of stay (log-transformed), as well as adjusted for time of onset, systolic blood pressure, initial CKD-EPI, and Glasgow-Blatchford. The results were expressed in exponential linear regression coefficient (eβ) and confidence interval. Statistical significance was evaluated by the Wald test and the goodness of fit of the models was presented as a percentage value of the R and R2 indices. Data were analyzed using the IBM SPSS computer program version 28.0 (SPSS Inc., Chicago, IL, USA) and p values <0.05 indicated statistical significance.

3 RESULTS

One hundred and five patients met the study inclusion criteria in the study, with a mean age of 64.2 years and a predominance of males (66.7%). Few patients were diagnosed with cirrhosis (less than 7%) or heart failure (less than 13%) and about 2/3 presented with melena. Time from symptom onset to seeking medical care varied widely (3-480 hours), with a median of 24 hours.

The mean hemoglobin level was 8.7g/dL (2.6 – 16.4) at admission, and 48 (45.7%) patients received hemotransfusion (mean transfused bags: 1.2; 1-10). The most prevalent causes of bleeding were peptic ulcers, followed by esophagitis and erosive gastritis. A minority of patients developed acute renal failure during hospitalization (17.6%) and approximately 1/3 required ICU admission.

The rate of new episodes of melena was approximately 15% and 19% of them required a new EGD, with 24% of all patients experiencing complications (acute renal failure or rebleeding). The mean hospitalization length was 8.1 days (1-37 days). These data can be verified in Table 1.

Table 1: Baseline characteristics of all patients

Variables		N	Results
Baseline			
Age		105	64,2 ± 18,8 (18 - 106)
Sex	Male	105	70 (66,7)
	Female		35 (33,3)
Aspirin	Yes	105	22 (21)
	No		83 (79)
Anticoagulant	Yes	105	14 (13,3)
	No		91 (86,7)
Melena	Yes	105	68 (64,8)
	No		37 (35,2)
Syncope	Yes	105	17 (16,2)
	No		88 (83,8)
Cardiac Insufficiency	Yes	105	13 (12,4)
	No		92 (87,6)
Cirrhosis	Yes	105	7 (6,7)
	No		98 (93,3)
Symptom onset time		103	45,1; 24 (3 - 480)
Time to EGD		105	20,5; 12 (2 - 72)
Systolic Pressure		101	111,7 ± 23,2 (68 - 192)
Heart Rate		103	98,9 ± 21,1 (60 - 180)
Nasogastric Tube	Yes	104	41 (39,4)
	No		63 (60,6)
Hemoglobin		91	8,7 ± 3,4 (2,6 - 16,4)
Hematocrit		80	26,4 ± 9,7 (8,1 - 48,7)
Platelets		76	269,9; 242 (28 - 879)
Prothrombin Time		77	1,5; 1,2 (1 - 8,4)
Urea		79	82,4; 68 (15 - 352)
Creatinine		81	1,4; 0,9 (0,4 - 11,2)

Glasgow-Blatchford Score		77	11,9; 13 (0 - 19)
Glasgow-Blatchford dichotomized	5 or less	77	5 (6,5)
	6 or higher		72 (93,5)
CKD-EPI		81	72,5 ± 35,1 (4 - 145)
Evolution			
Final Urea		67	61,9; 36 (9 - 277)
Final Creatinine		68	1,2; 0,9 (0,3 - 4,9)
Final CKD-EPI		68	74,6 ± 33,9 (11 - 139)
Developed Acute Kidney Injure	Yes	68	12 (17,6)
	No		56 (82,4)
Admission to ICU	Yes	105	33 (31,4)
	No		72 (68,6)
UGB causes	Gastric Ulcer	105	46 (43,8)
	Duodenal Ulcer		15 (14,3)
	Erosive Esophagitis		17 (16,2)
	Erosive Gastritis		10 (9,5)
	Mallory-Weiss		8 (7,6)
	Neoplasm		2 (1,9)
	Others		7 (6,7)
Second-look EGD	Yes	105	20 (19)
	No		85 (81)
New Melena	Yes	104	15 (14,4)
	No		89 (85,6)
Units of blood component used		104	1,2; 0 (0 - 10)
Performed blood transfusion	Yes	105	48 (45,7)
	No		57 (54,3)
Outcomes			
Complications	Yes	104	25 (24)
	No		79 (76)
Lenght of stay (days)		105	8,1; 6 (1 - 37)

EGD, esophagogastroduodenoscopy; CKD-EPI, glomerular filtration rate by the CKD-EPI formula; ICU, intensive care unit; UGB, upper gastrointestinal bleeding.
Source: Authors.

Complaints of melena, anticoagulant use, lower systolic pressures at admission as well as admission to the intensive care unit were significantly associated with blood transfusion. The mean hospitalization length for these patients almost doubled, and the clinical presentation of new melena requiring a new EGD also increased significantly. Renal outcomes did not change with blood transfusion (Table 2).

Table 2: Final characteristics of patients according to BT or NBT

Variables		Group BT		Group NBT		P value
		n	Results	n	Results	
BASELINE CARACTERISTICS						
Age		48	67,8 ± 16 (22 - 96)	57	61,1 ± 20,4 (17 - 106)	0,065
Sex	1	48	32 (66,7)	57	38 (66,7)	1
	2		16 (33,3)		19 (33,3)	
AAS	Yes	48	14 (29,2)	57	8 (14)	0,091
	No		34 (70,8)		49 (86)	

Anticoagulant	Yes	48	11 (22,9)	57	3 (5,3)	0,010
	No		37 (77,1)		54 (94,7)	
Melena	Yes	48	37 (77,1)	57	31 (54,4)	0,024
	No		11 (22,9)		26 (45,6)	
Syncope	Yes	48	8 (16,7)	57	9 (15,8)	1
	No		40 (83,3)		48 (84,2)	
Cardiac Insufficiency	Yes	48	7 (14,6)	57	6 (10,5)	0,565
	No		41 (85,4)		51 (89,5)	
Cirrhosis	Yes	48	4 (8,3)	57	3 (5,3)	0,700
	No		44 (91,7)		54 (94,7)	
Symptom onset time		47	66,2; 24 (3 - 480)	56	27,5; 24 (6 - 96)	0,072
Time until EGD		48	20,9; 17,5 (2 - 72)	57	20,1; 12 (2 - 72)	0,982
Systolic pressure		47	102,5 ± 20,7 (68 - 147)	54	119,7 ± 22,4 (76 - 192)	<0,001
Heart rate		48	103 ± 21,8 (67 - 180)	55	95,3 ± 19,9 (60 - 150)	0,067
Nasogastric tube	Yes	48	26 (54,2)	56	15 (26,8)	0,005
	No		22 (45,8)		41 (73,2)	
Hemoglobin		46	6,3 ± 2,1 (2,6 - 12,1)	45	11,1 ± 2,7 (7 - 16,4)	<0,001
Hematocrit		41	19,9 ± 6,1 (8,1 - 37,3)	39	33,3 ± 7,8 (20,9 - 48,7)	<0,001
Platelets		39	244,2; 228 (51 - 742)	37	297; 264 (28 - 879)	0,047
Prothrombin Time		40	1,8; 1,3 (1 - 8,4)	37	1,1; 1,1 (1 - 1,7)	0,004
Initial urea		39	92,6; 86 (17 - 352)	40	72,4; 61,7 (15 - 226)	0,181
Initial creatinine		39	1,3; 1 (0,5 - 5,6)	42	1,5; 0,9 (0,4 - 11,2)	0,561
Glasgow blathford score		38	14,1; 13,5 (9 - 19)	39	9,7; 10 (0 - 19)	<0,001
Glasgow blatchford dichotomized	5 or less	38	0 (0)	39	5 (12,8)	0,055
	6 or higher		38 (100)		34 (87,2)	
Initial CKD-EPI		39	69 ± 32,8 (9 - 134)	42	75,8 ± 37,2 (4 - 145)	0,392
EVOLUTION						
Final Urea		35	69; 40 (14 - 277)	32	54,1; 35 (9 - 253)	0,514
Final Creatinine		36	1,3; 0,8 (0,3 - 4,9)	32	1,1; 0,9 (0,5 - 2,4)	0,685
Final CKD-EPI		36	75,5 ± 34 (11 - 130)	32	73,6 ± 34,3 (19 - 139)	0,823
Developed acute renal injury	Yes	36	4 (11,1)	32	8 (25)	0,203
	No		32 (88,9)		24 (75)	
Admission to UCI	Yes	48	28 (58,3)	57	5 (8,8)	<0,001
	No		20 (41,7)		52 (91,2)	
UGB causes	Gastric Ulcer	48	27 (56,3)	59	19 (33,3)	-

	Duodenal Ulcer		7 (14,6)		8 (14)	
	Erosive Esophagitis		4 (8,3)		13 (22,8)	
	Erosive Gastritis		3 (6,3)		7 (12,3)	
	Mallory-Weiss		2 (4,2)		6 (10,5)	
	Neoplasm		2 (4,2)		0 (0)	
	Others		3 (6,3)		4 (7)	
Second EGD	Yes	48	18 (37,5)	57	2 (3,5)	<0,001
	No		30 (62,5)		55 (96,5)	
New melena	Yes	47	13 (27,7)	57	2 (3,5)	<0,001
	No		34 (72,3)		55 (96,5)	
Blood transfused bags		47	2,7; 2 (0 - 10)	57	0; 0 (0 - 0)	-
OUTCOMES						
Complications	Yes	47	15 (31,9)	57	10 (17,5)	0,109
	No		32 (68,1)		47 (82,5)	
Hospital Length (days)		48	10,8; 8 (2 - 37)	57	5,8; 4 (1 - 29)	<0,001

Source: Authors.

After adjustment to the Glasgow Blacthford score, symptom onset time, systolic pressure, and CKD-EPI, blood transfusion was not associated with complications analyzed in this study (Table 3). The Glasgow-Blatchford score was associated with the probability of having complications, with an increment of 1 point in the score increasing the chance of a patient with UGB by 18.6% to develop complications.

Table 3: Outcomes adjusted to variables: Glasgow-Blacthford score, symptom onset time, systolic pressure, and CKD-EPI

Factors related to complications (acute renal injury / new melena)	n	OR (IC de 95%)	P value	HL model quality
Blood transfusion, adjusted to symptom onset time.				
Performed blood transfusion	102	2,547 (0,985-6,584)	0,054	4,870 (0,801)
Ref: did not performed				
Symptom onset time (hours)		0,751 (0,486-1,159)	0,195	
Blood transfusion, adjusted to Systolic pressure				
Performed blood transfusion	100	1,453 (0,534-3,952)	0,464	8,699 (0,368)
Ref: did not performed				
Systolic pressure (mmHg)		0,982 (0,960-1,005)	0,128	
Blood transfusion, adjusted to Initial CKD-EPI				
Performed blood transfusion	80	1,844 (0,698-4,873)	0,217	9,695 (0,287)
Ref: did not performed				
Initial CKD-EPI		0,998 (0,984-1,012)	0,739	

Blood transfusion, adjusted to Glasgow Blatchford score				
Performed blood transfusion Ref: did not performed Glasgow Blatchford	76	0,70 (0,241-2,466) 1,0207 (1,024-1,421)	0,660 0,025	4,773 (0,888)

Source: Authors.

After adjusted for time of onset of symptoms, systolic pressure and CKD-EPI, blood transfusion remains associated with increased length of hospital stay. However, if adjusted to Glasgow Blatchford score, it loses significant association with the outcome (Table 4).

Table 4: Length of hospital stay after adjustment to symptom onset time, systolic pressure, CKD-EPI and Glasgow Blatchford score

Factors related to lenght of stay	n	e^{β} (IC de 95%)*	P Value#	% do R	% do R^2
Blood transfusion, adjusted to symptom onset time.					
Performed blood transfusion Ref: did not performed Symptom onset time (hours)	103	1,991 (1,477 | 2,684) 1,025 (0,894 | 1,175)	<0,001 0,722	43,0%	18,5%
Blood transfusion, adjusted to Systolic pressure					
Performed blood transfusion Ref: did not performed Systolic pressure (mmHg)	101	1,902 (1,393 | 2,598) 1,002 (0,995 | 1,008)	<0,001 0,637	39,4%	15,5%
Blood transfusion, adjusted to Initial CKD-EPI					
Performed blood transfusion Ref: did not performed Initial CKD-EPI	80	1,813 (1,283 | 2,561) 0,996 (0,991 | 1,001)	0,001 0,123	40,5%	16,4%
Blood transfusion, adjusted to Glasgow Blatchford score					
Performed blood transfusion Ref: did not performed Glasgow Blatchford score	76	1,514 (1 | 2,291) 1,038 (0,988 | 1,092)	0,050 0,139	38,8%	15,1%

Source: Authors.

4 DISCUSSION

In this study, blood transfusion was associated with a higher hospitalization length, higher rates of rebleeding requiring a new EGD, and greater severity of general clinical presentation. There was no positive or negative association with renal outcomes.

Blood transfusion has been associated with worst outcomes in patients with non-variceal upper GI Bleeding, particularly in those with baseline Hb levels greater than 10 g/dL (11). Higher rates of rebleeding rates and hospitalization length were associated with blood

transfusion in this study, probably due to the severity of clinical status of patients. Higher levels of anemia, lower blood pressure, higher heart rate, and the need for blood transfusion have already been shown to be risk factors for death in these patients (12).

In this scenario, blood transfusion could be stared as a marker of severity, similar to the Glasgow-Blatchford score. This hypothesis is corroborated by the loss of association with length of stay after adjusting for the Glasgow Blatchford score. Glasgow Blatchford score seems to be the most accurate tool in identifying patients who will require hospital-based intervention and those suited for early discharge and outpatient care (13).

The ideal hemoglobin target for blood transfusion in stable patients was not evaluated in this study. According to current scientific evidence, stable gastrointestinal bleeding patients should be transfused when hemoglobin levels reach below 7.0 g/dL, with transfusion at higher hemoglobin levels associated with worse outcomes (2,8). Possible explanations for this phenomenon are changes in the mechanism of splanchnic vasoconstriction with increased portal pressure and changes in the coagulation cascade. (9, 10).

Other hypothesis discussed in the literature is the blood transfusion complications – such as allergic reactions, pulmonary edema, and rebleeding – which could prolong hospitalization (2, 6). Overall complication rates in patients who received blood transfusions compared with those who did not are approximately 20% higher, and may double the rebleeding rate (14, 15).

It's important to emphasize that hemodynamically unstable patients were not excluded in our study, which may have contributed to more severe patients being included in the group that received blood transfusions. Another caveat that must be made is the lack of some data in the analyzed medical records. Their absence was proportionally adjusted for statistical analysis.

No change was found concerning to renal outcomes. However, correlation with greater clinical severity, rebleeding rates, and increased length of hospital stay have been found. It is not possible to prove a causal relationship, but the hypothesis that blood transfusion is a marker of severity, similar to the Glasgow-Blatchford score, must be considerated. The loss of association with length of stay when adjusted by the Glasgow-Blatchford score is in favor of this hypothesis.

5 CONCLUSION

In this study, blood transfusion was associated with longer hospital stay, global clinical severity and rate of rebleeding with new need for EGD; but was not associated with worse renal outcomes. It is possible that the need for blood transfusion is an isolated marker of severity, associated with worse outcomes, but it is not possible to establish causality.

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