

# Restrictive versus Liberal Blood Transfusion Strategies in Egyptian Patients with Esophageal Variceal Bleeding

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## Abstract

**Background and Study Aim:** Esophageal variceal bleeding is a major medical emergency and one of the most important indications for hospital admission and for blood transfusion. However, the safest and the effective blood transfusion strategy is controversial. Here, we studied the safety and the effectiveness of the restrictive versus liberal transfusion strategies in patients with esophageal variceal bleeding. **Patients and Methods:** The study included 342 patients with esophageal variceal bleeding. Patients were divided into 2 groups: group I (Restrictive strategy) transfusion when the hemoglobin level is  $\leq 7$  g/dl and group II (Liberal strategy): transfusion when the hemoglobin level is  $\leq 9$  g/dl. All patients were subjected to complete blood counts, liver and kidney profiles, coagulation profile, pelvi-abdominal ultrasonography and upper GI endoscopy. Clinical outcome measures include rebleeding, infection, allergic transfusion reactions thromboembolic events, and mortality. **Results:** Of all patients admitted to hospital with esophageal variceal bleeding, the number of transfused RBCs units and hospital stay were more in the liberal transfusion strategy. Also, the overall rate of complications was higher in the liberal transfusion strategy (49.7% versus 38.5% in the restrictive transfusion strategy). The most common complications were rebleeding (26.9%) and infection (21.6%). As regard the death rate, 13 cases (7.6%) died in the restrictive transfusion strategy versus 25 cases (14.6%) in the liberal transfusion one. **Conclusions:** For esophageal variceal bleeding, restrictive transfusion strategy is better than the liberal one as regard cost-effectiveness, risk of complications and hospital stay with no harm and less mortality as compared to liberal strategy.

## Keywords

Esophageal Variceal Bleeding, Blood Transfusion, Restrictive Strategy, Liberal Strategy

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## 1. Introduction

Esophageal variceal bleeding is a major medical emergency and one of the most important indications for hospital admission. It has a mortality rate of 20% - 25% [1] [2]. In Egypt, it was estimated that esophageal varices develop in about 50% - 63% of patients with liver cirrhosis and portal hypertension [3] [4]. The strongest predictor for development of varices in cirrhosis is a hepatic venous pressure gradient (HVPG) equal or more than 10mmHg [5] [6], but variceal bleeding does not occur until the HVPG increases above 12 mmHg [7] [8].

Acute variceal bleeding is a main indication for red blood cells (RBCs) transfusion; because acute anemia which occurs due to bleeding is associated with increased mortality. This is most likely related to impaired oxygen delivery and tissue hypoxia. The mortality rate in acute anemia is directly related to the decrease in hemoglobin. However, in some cases blood loss is not so severe, and in that condition the safest and most effective blood transfusion strategy is controversial [9] [10].

In most cases, RBCs are transfused when the hemoglobin level has decrease to a threshold at which the physician believes the risks of anemia is more than the risks of blood transfusion. This perception of the suitable level for transfusion is subjective but is influenced by multiple factors including the desire to have a safe hemoglobin level to prevent rebleeding and decrease symptoms of anemia after stoppage of bleeding [11] [12].

A restrictive transfusion strategy (RTS) was defined as transfusion(s) for GI bleeding when the hemoglobin level is less than seven grams/dl. And, a liberal transfusion strategy (LTS) was defined as transfusion(s) when hemoglobin level falls below nine grams/dl [13].

Restrictive transfusion strategy may be more effective in some situations. Experimental trials concluded that for critically ill patients, restrictive transfusion of blood is as good as liberal transfusion and more over it reduces need for blood supplies. But these trials excluded cases with gastrointestinal bleeding [14] [15]. Furthermore, several experimental and clinical studies have shown that blood transfusion can be particularly harmful in cirrhotic patients with acute variceal bleeding, since restitution of blood volume can lead to a rebound increase in portal pressure, an increase that may be prevented with somatostatin, which is associated with increasing risk of rebleeding [16]-[19].

The aim of this study was to assess the safety and the effectiveness of the restrictive versus liberal transfusion strategies in patients with esophageal variceal bleeding.

## 2. Patients and Methods

This clinical interventional study was carried out at Tropical Medicine Department, Zagazig University Hospitals, Egypt, during a period from June 2015 to November 2015. This study was approved by Ethical Committee of Faculty of Medicine, Zagazig University, including the informed consents which were obtained from all patients. There were no conflicts of interests and no funding during the study.

Patients with esophageal variceal bleeding who presented to the intensive care unit were included in the study. Patients were excluded if they refuse blood transfusion or if they have upper gastrointestinal bleeding of any cause other than esophageal varices.

According to the inclusion and the exclusion criteria, 342 patients with esophageal variceal bleeding (249 males and 93 females), their ages ranged from 34 to 65 years old ( $51.602 \pm 7.403$ ) were included in this study. Patients were divided into 2 groups: **Group I (Restrictive Transfusion strategy-RTS)**: consisted of 171 patients (127 males and 44 females). Participants allocated to this group were eligible for blood transfusion when their Hb level is  $\leq 7$  g/dl. The objective was to maintain the Hb level between 7.1 - 9 g/dl; **Group II (Liberal Transfusion strategy-LTS)**: consisted of 171 patients (122 males and 49 females). Participants allocated to this group were eligible for transfusion when their Hb level is  $\leq 9$  g/dl. The objective was to maintain the Hb level between 9.1 - 11g/dl.

### Methods:

Patients were subjected to:

- 1) Detailed history taking.
- 2) Thorough clinical examination.
- 3) Laboratory investigations (complete blood counts, liver and kidney profiles, coagulation profile).
- 4) Pelvi-abdominal ultrasonography and Doppler study of the portal vein (Esaote MyLab20Plus).
- 5) Upper GI endoscopy (PENTAX VIDEO endoscopy): endoscopy was done within 24 hours of admission.

**Treatment Program:**

In both groups, hemoglobin level was measured immediately after hospital admission and every 12 hours during the first 48 hours and every 24 hours after that. Units of packed RBCs were transfused to reach the target level of Hb.

**The outcome:**

The outcome include in hospital complications, number of blood units transfused and duration of hospital stay. The complications include the following (from day zero to day 14 or until patient's discharge):

- 1) Detection of another gastrointestinal bleeding (rebleeding).
- 2) Infection (This is defined as any infection necessitating a prescription for antibiotic treatment for a minimum of 5 days).
- 3) Blood transfusion reactions (for example, febrile transfusion reactions, allergic transfusion reaction, transfusion transmitted infections, transfusion-related acute lung injury).
- 4) Patients experiencing thrombo-embolic and ischemic events (myocardial ischemia or infarction, cerebrovascular stroke, pulmonary embolism, deep venous thrombosis, and acute renal failure).
- 5) Death rate.

**Statistical analysis:**

Data were checked, entered and analyzed using SPSS version 19 for data processing and statistic. Data were expressed as mean  $\pm$  SD for quantitative variable, number and percentage for qualitative one. Chi-squared ( $X^2$ ) or student "t" test were used when appropriate.  $P < 0.05$  was considered significant.

**3. Results**

In this study, no statistical significant differences were observed among both studied groups with respect to patients' age and sex (**Table 1**). As regard laboratory parameters in this study, WBCs were significantly more in the liberal transfusion group ( $P = 0.00$ ). While, INR level and prothrombin time were significantly more in the restrictive transfusion group ( $P = 0.004$  and  $0.04$  respectively).

According to endoscopic data of the studied groups; higher grades of O.V. (grade III and IV) ( $P = 0.009$ ) and more risky signs ( $P = 0.013$ ) were detected in the restrictive transfusion group (**Table 2**).

Regarding blood transfusions and hospital stay; number of RBCs units transfused was significantly more in the liberal transfusion group (the mean in group I was 1.2 versus 1.8 in group II with  $P = 0.002$ ). While, number of fresh frozen plasma units transfused was significantly more in the restrictive transfusion group (the mean in group I was 2.5 versus 1.4 in group II with  $P = 0.004$ ). Furthermore, patients who were under liberal transfusion strategy stayed more days at hospital (the mean in group I was 4.5 versus 5.4 in group II with  $P = 0.002$ ) (**Table 3**).

Concerning the study outcome as shown in **Table 4** and **Figure 1**, the overall rate of complications was statistically significant higher in the liberal transfusion group (49.7% versus 38.5% in the restrictive transfusion group) ( $P = 0.03$ ). Cardiac complications, stroke and TIA, acute kidney injury and allergic reactions due to blood component were comparable in both groups. While the rates of rebleeding and infection were statistically significant higher in the liberal transfusion group (26.9%,  $P = 0.03$  and 21.6%,  $P = 0.005$  respectively). As regard the death rate, there was statistically significant difference between both studied groups ( $P = 0.03$ ). Thirteen cases (7.6%) died in the restrictive transfusion group versus 25 cases (14.6%) in the liberal transfusion one.

**Table 1.** Baseline characteristics among both studied groups.

	Group I (RTS) (n = 171)		Group II (LTS) (n = 171)		t	P
Age						
Mean ± SD	51.47 ± 8.81		51.17 ± 8.10		0.332	0.740
	No.	%	No.	%	X²	P
Gender						
Male	127	74.3	122	71.3	0.36	0.54
Female	44	25.7	49	28.7		

**Table 2.** Endoscopic data among both studied groups.

		Group I (RTS) (n = 171)		Group II (LTS) (n = 171)		X <sup>2</sup>	P
		No	%	No	%		
Endoscopic findings	O.V. grades	Grade I	17	9.9	8	4.7	11.6
		Grade II	116	67.8	143	83.6	
		Grade III	33	19.3	17	9.9	
		Grade IV	5	2.9	3	1.8	
	O.V. risky signs	No	118	69.0	138	80.7	6.21
		Yes	53	31.0	33	19.3	

\*P &lt; 0.05 is significant.

**Table 3.** Blood transfusions and duration of hospital stay among both studied groups.

		Group I (RTS) (n = 171)	Group II (LTS) (n = 171)	t	P
		Mean ± SD	Mean ± SD		
Units of RBCs transfused		1.2 ± 1.480	1.8 ± 1.743	-3.110	0.002*
Units of fresh frozen plasma transfused		2.5 ± 4.068	1.4 ± 3.121	2.878	0.004*
Duration of hospital stay		4.5 ± 1.840	5.4 ± 2.989	-3.137	0.002*

\*P &lt; 0.05 is significant.

**Table 4.** The study outcome among both studied groups.

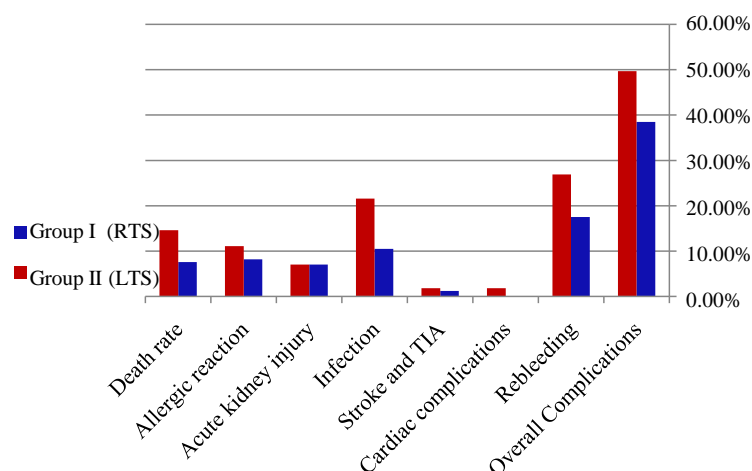
Outcome	Group I (RTS) (n = 171)		Group II (LTS) (n = 171)		X <sup>2</sup>	P
	No	%	No	%		
Overall rate of complications	66	38.5	85	49.7	4.28	0.03*
Rebleeding	30	17.5	46	26.9	4.33	0.03*
Infection	18	10.5	37	21.6	7.82	0.005*
Cardiac complications	0	0.0	3	1.8	3.02	0.08
Stroke and TIA	2	1.2	3	1.8	0.203	0.65
Acute kidney injury	12	7.0	12	7.0	0.00	1.00
Allergic reactions	14	8.2	19	11.1	0.83	0.36
Death rate	13	7.6	25	14.6	4.26	0.03*

\*P &lt; 0.05 is significant.

## 4. Discussion

Acute variceal bleeding (AVB) is the most common cause of acute upper gastrointestinal bleeding (AUGIB) in patients with cirrhosis [20]. Current RBCs transfusion concepts in AUGIB depend on consensus opinion. The international guideline recommends transfusion when the hemoglobin is  $\leq 7$  gm/dl [10]. For those with AUGIB due to portal hypertension, guidelines recommend keeping the hemoglobin level around 8 gm/dl [21]. In this study, two transfusion strategies were compared; the restrictive transfusion strategy in which the hemoglobin threshold for transfusion was  $\leq 7$  g/dl, with a target range to maintain the hemoglobin level between 7.1 - 9 g/dl; and the liberal transfusion strategy in which the hemoglobin threshold for transfusion was  $\leq 9$  g/dl, with a target range to maintain the hemoglobin level between 9.1 - 11 g/dl.

The present study showed statistically significant increase in number of RBCs units transfused in LTS group (mean = 1.8 vs. 1.2 in the RTS group, P = 0.002). This is consistent with Villanueva and his colleagues which showed significantly more RBCs units transfused in LTS group (mean = 3.7) than RTS group (mean = 1.5) (P =



**Figure 1.** Study outcomes from the studied groups.

0.01) [13]. On the other hand, this study revealed that the number of plasma units transfused was significantly higher in RTS group (mean = 2.5 vs. 1.4 in LTS group,  $P = 0.004$ ). These results are in disagreement with **Villanueva *et al.*** which had more plasma units transfused in the LTS group (41 units of plasma transfused vs. 28 in the RTS group,  $P = 0.13$ ). This disagreement may be attributed to the higher INR level of RTS group in this study (mean = 2.2 vs. 1.4 in the LTS group,  $P = 0.004$ ) [13].

As regard complications, it was found that the overall rate of complications was higher in the LTS group (49.7% of LTS group vs. 38.5% of RTS group), with statistically significant difference between both groups ( $P = 0.03$ ). These results are in agreement with **Al-Jaghbeer and Yende [22]**, and **Villanueva *et al.* [13]**. Both studies rated more complications in the LTS group (48% of LTS group vs. 40% of RTS group,  $P = 0.02$ ).

Previous studies reported more rebleeding in patients of LTS group; 16% of LTS group vs 10% of RTS group,  $P = 0.01$  [22] and 22% of LTS group vs. 11% of RTS group,  $P = 0.05$  [13]. Our results, which are consistent with the results from those studies, showed that despite the presence of more cases with larger varices (grade III, 19.3% and grade IV, 2.9%) and more risky signs (31.0%) in the RTS group, rebleeding occurred more with LTS group (26.9% of LTS group vs. 17.5% of RTS group,  $P = 0.03$ ). This may be related to excessive RBCs transfusion which is likely increase portal pressure through volume overload, in patients of liver cirrhosis and bleeding esophageal varices, with increasing the risk of rebleeding [13] [17]. Also, Transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia, inducing an increase in splanchnic blood flow and pressure that may impair the formation of clots [23] [24].

As regard hospital stay, it was found that patients of LTS group stayed more days at hospital (mean = 5.4) than patients of RTS group (mean = 4.5) with statistically significant difference ( $P = 0.002$ ). These results are in agreement with **Villanueva and his colleagues** which showed more hospital stay in LTS group ( $P = 0.01$ ). This result may be due to higher rate of complications, especially rebleeding, in the LTS group [13]. Furthermore, it was found that infection was significantly higher ( $P = 0.005$ ) in LTS group (21.6%) than in RTS group (10.5%) which may be attributed to more hospital stay in the LTS group which makes the patient at more risk for hospital acquired infection.

Also, this study showed that the death rate was more in LTS group (14.6% in LTS vs. 7.6% in RTS), with statistically significant difference between the two groups ( $P = 0.03$ ). These results are consistent with results from previous studies performed in other settings, which found that a restrictive transfusion strategy did not increase [15] [25] and even decreased [14] [26] the mortality observed with a liberal transfusion strategy. Moreover, these findings are in agreement with the findings of **Villanueva *et al.*** in which all patients with cirrhosis had lower risk of death in the RTS group than the LTS group [13]. Similar results were obtained by **Al-Jaghbeer and Yende** which concluded that probability of survival at 6 weeks was higher in the RTS group than in the LTS group (95% versus 91%) ( $P = 0.02$ ) [22]. These results may be related to lower rate of serious complications in RTS group, such as infection and rebleeding, which need urgent therapy.

From the present study and its results, we can summarize that the outcome among patients with esophageal variceal bleeding is better with a restrictive transfusion strategy, as compared with a liberal transfusion strategy.

## 5. Conclusion

For esophageal variceal bleeding, restrictive transfusion strategy is better than the liberal one as regard cost-effectiveness, risk of complications and hospital stay with no harm and less mortality as compared to liberal strategy.

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