Comparison of 2 Days versus 5 Days of Octreotide after Endoscopic Therapy in Preventing Early Esophageal Varices Rebleed: A Randomized Controlled Study

Mennat-Allah Mohamed El Sawaf*, Hanan Hamed Soliman, Asem Ahmed Elfert, Lobna Ahmed Abo Ali, Samah Mosaad Soliman, Boshra Elsayed Talha Hussein

Tropical medicine and infectious diseases Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

In esophageal varices bleeding, following the initial endoscopic hemostasis, it is recommended to administer vasoactive medications for a period of 2-5 days in order to avoid early rebleeding. Octreotide is the preferred vasoactive medication for treating variceal bleeding due to its favorable safety profile. This study aimed to assess the effectiveness of a 2-day octreotide infusion against a 5-day octreotide infusion following endoscopic intervention in avoiding early rebleeding of esophageal varices in individuals with cirrhosis. This study was a prospective, parallel, randomised controlled experiment conducted on a cohort of 184 subjects who were recruited from the endoscopy unit of the Tropical Medicine and Infectious Diseases Department at Tanta University Hospital in Egypt. The five days rate of rebleeding was 16.85% in the 2-days group against 15.91% in the 5- days group without significant difference (P= 0.865). In cirrhotic individuals with bleeding esophageal varices, a 2-day regimen of octreotide is equally efficacious as a 5-day regimen in avoiding rebleeding over a 5-day period, following successful control of bleeding with endoscopic intervention.

1. Introduction

Acute variceal bleeding is a serious complication that can occur in individuals with cirrhosis. It is crucial to promptly and effectively manage this condition in order to avoid further episodes of bleeding. The primary focus of managing acute variceal bleeding is to ensure sufficient perfusion and oxygenation of the body's organs while attaining hemostasis, while also avoiding any further increase in portal pressure [1]. It is recommended to start administering vasoactive medications promptly upon suspicion or confirmation of variceal hemorrhage, ideally before any diagnostic or therapeutic endoscopic procedures [2]. Following the initial endoscopic hemostasis, it is recommended to administer vasoactive medications for a period of 2-5 days in order to avoid early rebleeding. Octreotide is the preferred vasoactive medication for treating variceal bleeding due to its favorable safety profile [3].

2. Materials and Methods

This study was a prospective, parallel, randomized controlled experiment conducted on a cohort of 184 subjects who were recruited from the endoscopy unit of the Tropical Medicine and Infectious Diseases Department at Tanta University Hospital in Egypt. It began in June 2019 and ended October 2022 (recruitment and follow-up). The participants had been assigned at random into 2-days octreotide group (92 patients) or 5-days octreotide group (92 patients) finally, 89 participants were included for analysis in the 2-days octreotide group versus 88 participants in the 5-days octreotide group.

Inclusion criteria

- Age ≥18 years.
- Acute esophageal variceal bleeding.
- Cirrhotic liver.

Exclusion criteria

- Initial inability to manage variceal hemorrhage during endoscopy.
- Additional factors contributing to gastrointestinal hemorrhage.
- Hepatocellular carcinoma.
- Thrombosis in the portal vein.
- Hepatorenal syndrome and renal dialysis.
- Ischemic heart disease.
- Pregnancy or lactation.
- Allergy to octreotide.

2.1. Sample size calculation and study design

This was a parallel, prospective, randomized controlled experiment. The participants had been assigned at random into 2-days octreotide group or 5-days octreotide group. The participants involved in the study were randomly assigned utilizing a computer random number generator. The randomization was done utilizing permuted blocks with varying block sizes of 4, 6, and 8. The allocation ratio was same for all blocks. Concealment was ensured by using envelopes that were sequentially numbered, opaque, and sealed [4].

2.2. Outcomes

Primary outcome

- 5-days rebleeding rate.

Secondary outcomes

- 5-days mortality rate.
- 6-weeks mortality rate.
- 6-weeks rebleeding rate.

All the patients in the study were subjected to the following

- Comprehensive taking of history
- Thorough clinical examinations.
- 3-Laboratory investigations.
- Abdominal ultrasonography and electrocardiogram.
- Modified Child-Pugh, MELD and Glasgow-Blatchford bleeding scores
- Upper endoscopy to detect and control variceal bleeding.

Follow-up

Each participant had to be hospitalized for a minimum of 5 days following the initial bleeding event. They were only discharged if there were no other medical reasons for keeping them in the hospital. Upon discharge, each participant were initiated on nonselective beta-blockers, unless contraindicated. The individuals were instructed to go to the hospital if they observed any signs of hematemesis or melena. Outpatient follow-up appointments were scheduled at 3 and 6 weeks following the initial bleeding event in order to evaluate secondary consequences.

2.3. Statistical analysis

The statistical data were provided as the mean ± SD, frequency (number), and percentage as deemed appropriate. The research groups have been contrasted utilizing Student's t-test, which is employed for comparing independent samples from both groups when the samples follow a normal distribution. χ^2-test was performed to compare categorical data, and Outcome measures. Multivariate logistic analysis had been performed utilising a logistic regression model to determine independent indicators for 5-days rebleeding. To calculate the cutoff values that may predict rebleeding, receiver operating characteristic (ROC) curve was utilised. P-values ≤ 0.05 were considered statistically significant. The SPSS software program (Armonk, NY: IBM Corp) version 20 for Microsoft Windows was utilized for all statistical calculation

3. Results and discussion

As regards basic demographic data of the groups under the study, no substantial variation was existed (P>0.05). As regards baseline patients scores of the studied groups, no substantial variation was existed (P>0.05). No substantial variation had been existed among the studied groups as regards clinical characteristics (P>0.05). No substantial variation had been existed among the studied groups as regards laboratory investigations(P>0.05). Baseline abdominal ultrasonographic data didn't demonstrate any substantial variation among groups(P>0.05). Baseline endoscopic data didn't demonstrate any substantial variation among groups (P>0.05). No substantial variation had been existed among the studied groups as regards 5- days rebleeding rate (primary outcome), 5-days mortality rate, 6-weeks mortality rate and 6- weeks rebleeding rate (secondary outcomes) (P>0.05). In the current study, 5-days rebleeding rate was 16.85% in our patients who received 2 days of octreotide and 15.91% in patients who received 5 days of octreotide. These results were in agreement with [5] .compared the results of participants undergoing early (≤12 hours) against late (>12 hours) endoscopic procedures for acute bleeding from esophageal varices and found that 5 days rebleeding rate was 16.5% in early endoscopy group against 24.2% in late group. This was in accordance with [6] .study who compared the effectiveness of a 2-day against a 5-day octreotide infusion, alongside endoscopic intervention, in avoiding early rebleeding from esophageal varices. The study revealed that a 2-day infusion of octreotide was adequate or at least equally effective to 5-day infusion in avoiding early rebleeding and mortality. Additionally, the 2-day infusion was found to be more cost-effective. However, in their study, early rebleeding among the patients in the 2-days group was 4.8% versus 8.6% in the 5-days group which is lower than our results. This may be related to different inclusion and exclusion criteria as they included both cirrhotic and non-cirrhotic patients, younger age (13 years and older, average 47 years) and exclude patients with previous endoscopic therapy. In the present study, 6-weeks rate of rebleeding was 6.74% in the 2 days group against

10.23% in the 5 days group with endoscopy done in first 24 hours in all patients.

Table 1. Basic demographic data of the studied groups

Parameters		Group I 2-Days (N=89)			Group II 5-Days (N=88)			X^2	P-value
Age (years)	Range	40	-	79	42	-	75	-0.454[a]	0.650
	Mean ±SD	59.427	±	7.236	59.932	±	7.553		
		N		%	N		%		
Gender	Female	32		35.96	29		32.95	0.176	0.675
	Male	57		64.04	59		67.05		
Diabetes		22		24.72	28		31.82	1.100	0.294
Previous upper GIT bleeding		49		55.06	52		59.09	0.294	0.588
History of blood transfusion		30		33.71	30		34.09	0.003	0.957
History of hepatic encephalopathy		36		40.45	35		39.77	0.008	0.927
Beta blockers	No	35		39.33	40		45.45	1.004	0.605
	Carvedilol	42		47.19	35		39.77		
	Propranolol	12		13.48	13		14.77		

a= t test; X^2= chi-square; N, number; SD, standard deviation; GIT, gastrointestinal; significant P≤0.05*.

Table 2. Baseline patients scores of the studied groups

Parameters		Group I		Group II		X^2	P-value
		2-Days (N=89)		5-Days (N=88)			
		N	%	N	%		
Child-Pugh class	Child A	14	15.73	11	12.50	0.622	0.733
	Child B	40	44.94	38	43.18		
	Child C	35	39.33	39	44.32		
Child-Pugh score	Range	5 – 13		6 – 13		-0.073[a]	0.942
	Mean ±SD	9.135 ± 2.341		9.159 ± 2.084			
MELD score	Range	7 - 36		6 - 27		-0.076[a]	0.946
	Mean ±SD	15.640 ± 6.739		15.580 ± 5.069			
Glasgow-Blatchford score	Range	3 - 17		4 - 17		-0.003[a]	0.997
	Mean ±SD	10.124 ± 2.954		10.125 ± 2.884			

a= t test, X^2= chi-square; N, number; SD, standard deviation; MELD, model of end stage liver disease; significant P≤0.05*.

Table 3. Clinical characteristics of the studied groups

Parameters		Group I		Group II		X^2	P-value
		2-Days (N=89)		5-days(N=88)			
		N	%	N	%		
Presenting complaint	Hematemesis	36	40.45	32	36.36	0.976	0.614
	Melena	35	39.33	41	46.59		
	Both	18	20.22	15	17.05		
Jaundice		44	49.44	41	46.59	0.144	0.705
Ascites	No	25	28.09	18	20.45	1.997	0.573
	Mild	22	24.72	24	27.27		
	Moderate	28	31.46	27	30.68		
	Severe	14	15.73	19	21.59		
Lower limb edema	No	8	8.99	4	4.55	1.400	0.705
	Mild	15	16.85	15	17.05		
	Moderate	34	38.20	36	40.91		
	Severe	32	35.96	33	37.50		
Pulse (b/m)	Range	70 - 112		75 - 123		-0.318[a]	0.751
	Mean ±SD	95.416 ± 8.997		95.864 ± 9.732			
SBP (mmHg)	Range	70 - 130		80 - 130		1.641[a]	0.103
	Mean ±SD	104.607 ± 12.585		101.932 ± 10.041			
DBP (mmHg)	Range	50 - 90		50 - 80		0.894[a]	0.372
	Mean ±SD	65.955 ± 9.620		64.773 ± 7.875			

a= t test; X^2= chi-square; DBP, diastolic blood pressure; SBP, systolic blood pressure; b/m, beat per minute; N, number; standard deviation; significant P≤0.05*
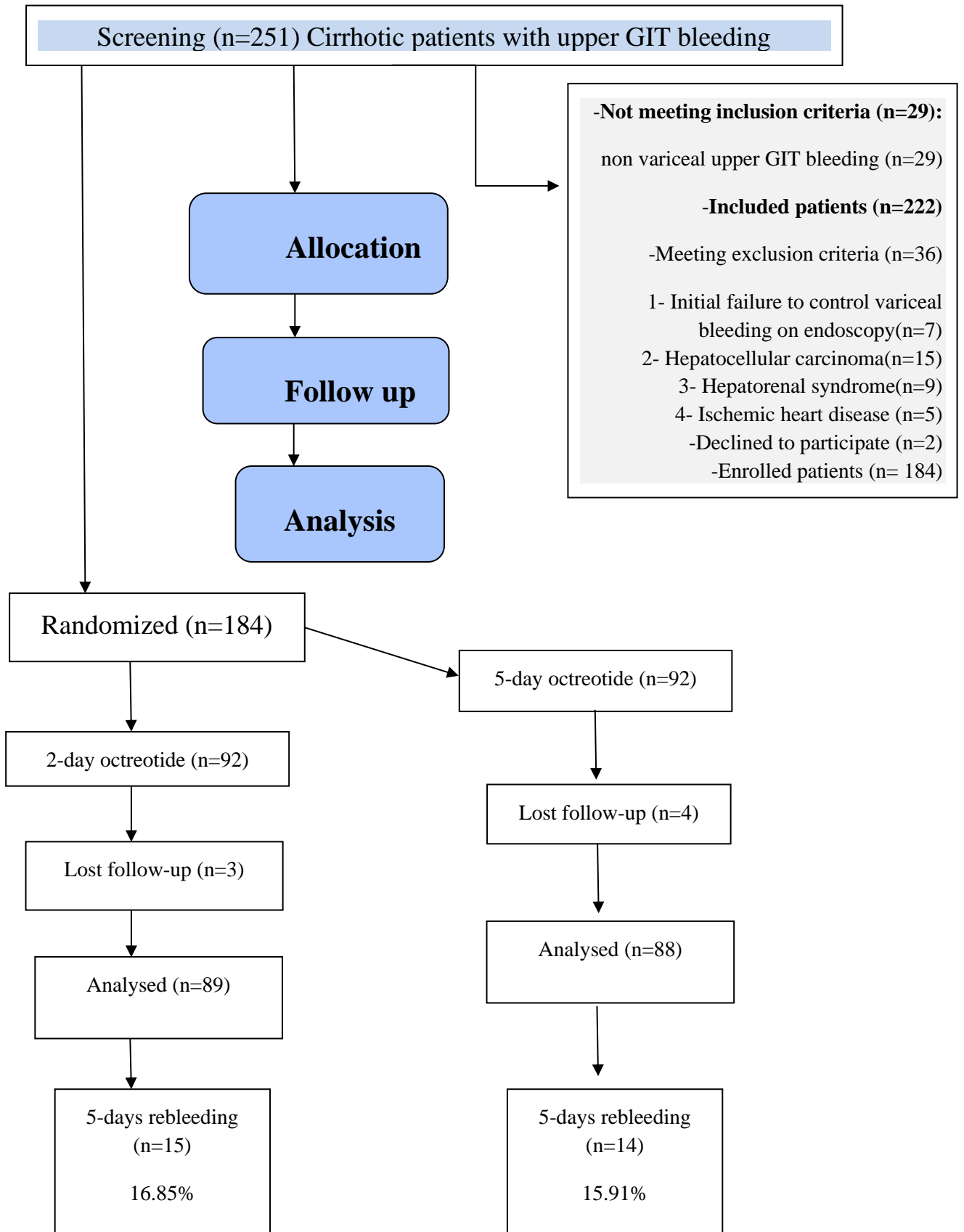
Figure 1. Study flow chart

**Table 4.** Baseline laboratory investigations of the studied groups

Parameters		Group I			Group II			T-Test	
		2-Days (N=89)			5-Days (N=88)			T	P-value
Hb (g/dl)	Range	5.8	-	12.2	4.8	-	12.1	-1.421	0.157
	Mean ±SD	8.901	±	1.438	9.215	±	1.497		
WBCs (x10^3 /mm^3)	Range	2.8	-	24.8	2.1	-	23.9	-0.707	0.481
	Mean ±SD	6.210	±	3.374	6.566	±	3.323		
Platelets (x10^3 / mm^3)	Range	35	-	135	42	-	160	-0.465	0.642
	Mean ±SD	89.112 ± 20.425			90.625 ± 22.772				
Total bilirubin	Range	0.7	-	15.7	0.4	-	9.2	1.122	0.263
(mg/dl)	Mean ±SD	3.160 ± 2.653			2.774 ± 1.855				
Serum Albumin	Range	1.8	-	3.5	1.8	-	3.4	1.095	0.275
(g/dl)	Mean ±SD	2.664 ± 0.402			2.605 ± 0.315				
AST	Range	14	-	272	13	-	425	-0.281	0.779
IU/L (up to 37)	Mean ±SD	67.517 ± 43.942			69.830 ± 63.801				
ALT	Range	10	-	293	10	-	315	-0.245	0.807
IU/L (up to 40)	Mean ±SD	43.348 ± 40.678			44.932 ± 45.232				
INR	Range	1	-	3.7	1	-	2.8	0.860	0.391
	Mean ±SD	1.622 ± 0.578			1.556 ± 0.429				
Serum creatinine (mg/dl)	Range	0.6	-	2.5	0.6	-	1.8	-0.306	0.760
	Mean ±SD	1.051 ± 0.330			1.066 ± 0.318				
BUN (mg/dl)	Range	9.8	-	70	9.33	-	81.2	-0.574	0.567
	Mean ±SD	20.281 ± 11.124			21.345 ± 13.437				
Urea (mg/dl)	Range	21	-	150	28	-	174	-0.357	0.722
	Mean ±SD	43.562 ± 23.853			46.943 ± 27.532				

Hb, hemoglobin; WBCs, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio; SD, standard deviation; significant P≤0.05.

Table 5. Baseline abdominal ultrasonographic data of the groups under the study

Parameters		Group I			Group II			X^2	P-value
		2-Days (N=89)			5-Days (N=88)				
P.V diameter (mm)	Range	11	-	18	11	-	19	0.547ᵃ	0.585
	Mean ±SD	15.466	±	1.858	15.322	±	1.653		
Spleen size (cm)	Range	12	-	19.5	13	-	19	0.445ᵃ	0.657
	Mean ±SD	15.923	±	1.748	15.815	±	1.309		
		N		%	N		%		
Cirrhotic liver		89		100.00	88		100.00	-	-
Portal vein patency		89		100.00	88		100.00	-	-
Splenectomy		5		5.62	8		9.09	0.784	0.376
Ascites	No	23		25.84	14		15.91	4.091	0.252
	Mild	15		16.85	20		22.73		
	Moderate	25		28.09	32		36.36		
	Severe	26		29.21	22		25.00		

a= t test; X^2= chi-square; N, number; PV diameter, portal vein diameter, SD, standard deviation; significant P≤0.05*.
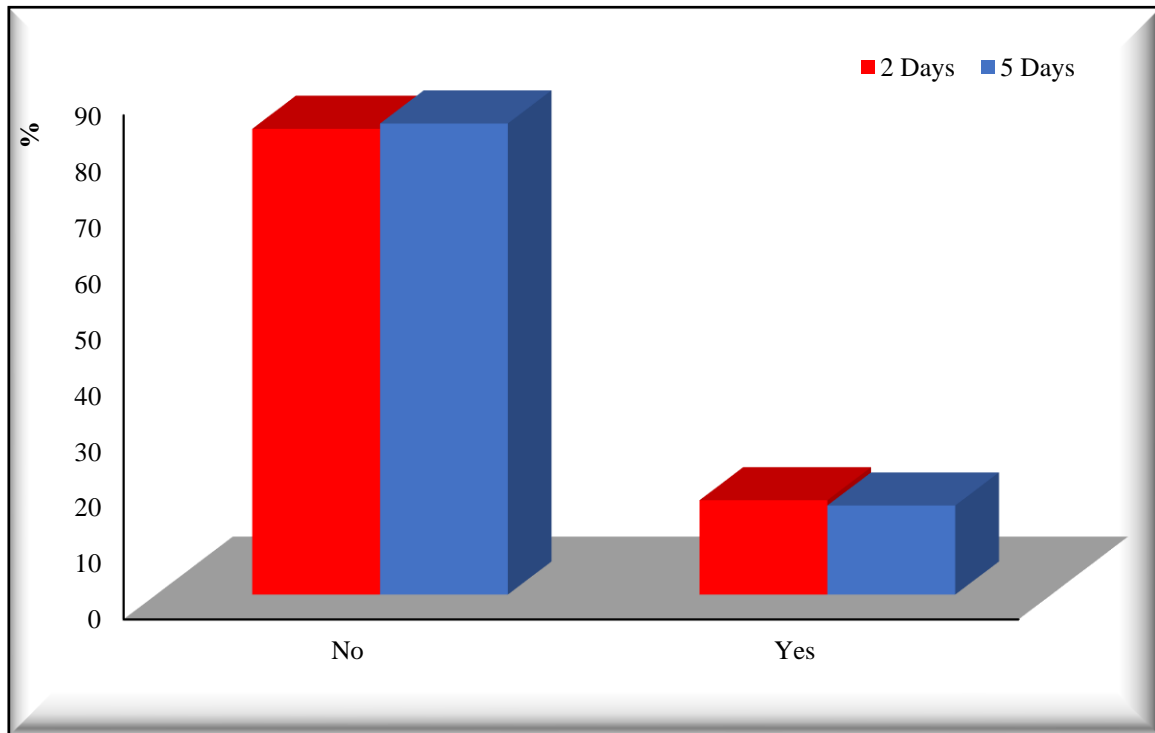
Figure 2. Five-days rebleeding rate

Table 6. Baseline endoscopic data of the studied groups

Parameters			Group				Chi-Square	
			2-Days (N=89)		5-Days (N=88)			
			N	%	N	%	X^2	P-value
Esophageal varices	Grade I		10	11.24	9	10.23	0.501	0.919
	Grade II		36	40.45	38	43.18		
	Grade III		37	41.57	37	42.05		
	Grade IV		6	6.74	4	4.55		
Risky esophageal varices	Non risky		32	35.96	33	37.50	0.045	0.831
	Risky		57	64.04	55	62.50		
Fundal varices	No fundal varices		53	59.55	54	61.36	0.423	0.809
	Fundal varices		20	22.47	22	25.00		
	Stomach full of blood		16	17.97	12	13.64		
Endoscopic therapy	Injection sclerotherapy		22	24.72	24	27.27	0.150	0.699
	Band ligation		62	69.66	58	65.91	0.286	0.593
	Scleroligation		5	5.62	6	6.82	0.109	0.741

X^2= chi-square; N, number; SD, standard deviation; significant P≤0.05*.

Table 7. Comparison of rebleeding and mortality between the studied groups

	Group I		Group II		Chi-Square	
	2-Days (N=89)		5-Days (N=88)			
	N	%	N	%	X^2	P-value
5- days rebleeding rate	15	16.85	14	15.91	0.029	0.865
5-days mortality rate	4	4.49	5	5.68	0.129	0.719
6-weeks mortality rate	8	8.99	7	7.95	0.061	0.805
6-weeks rebleeding rate	6	6.74	9	10.23	0.693	0.405

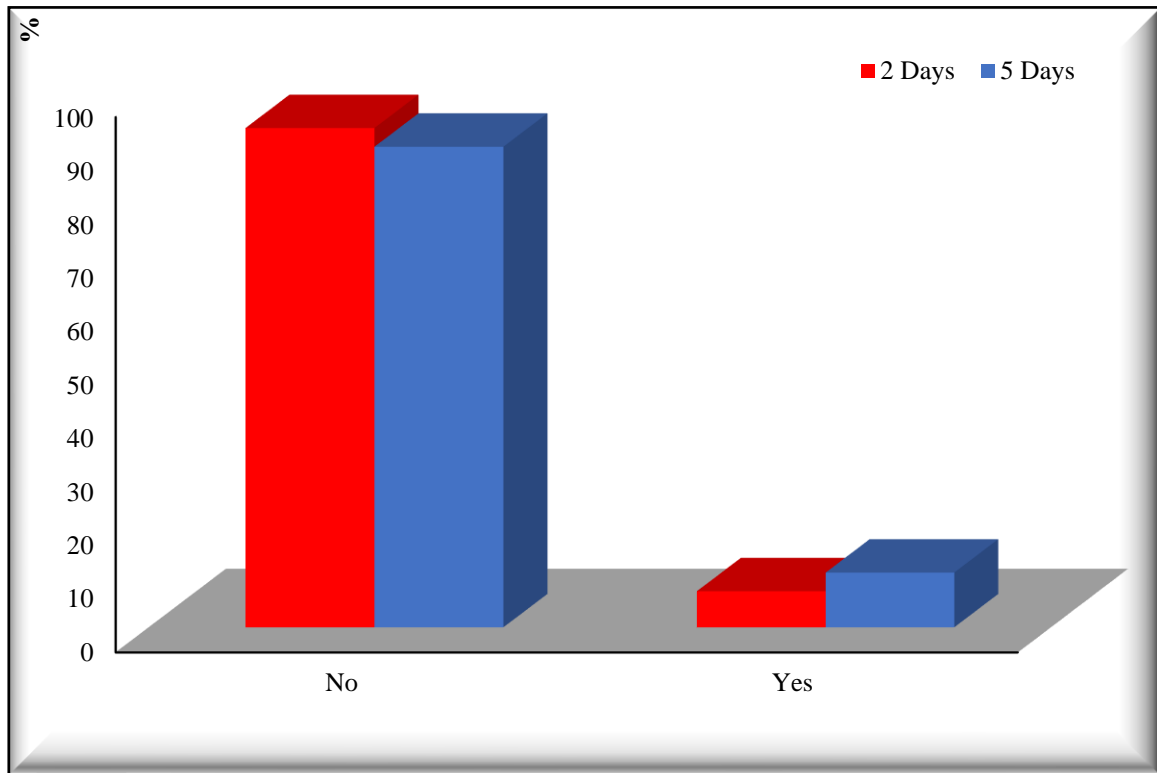X^2= chi-square; N, number; significant P≤0.05*.

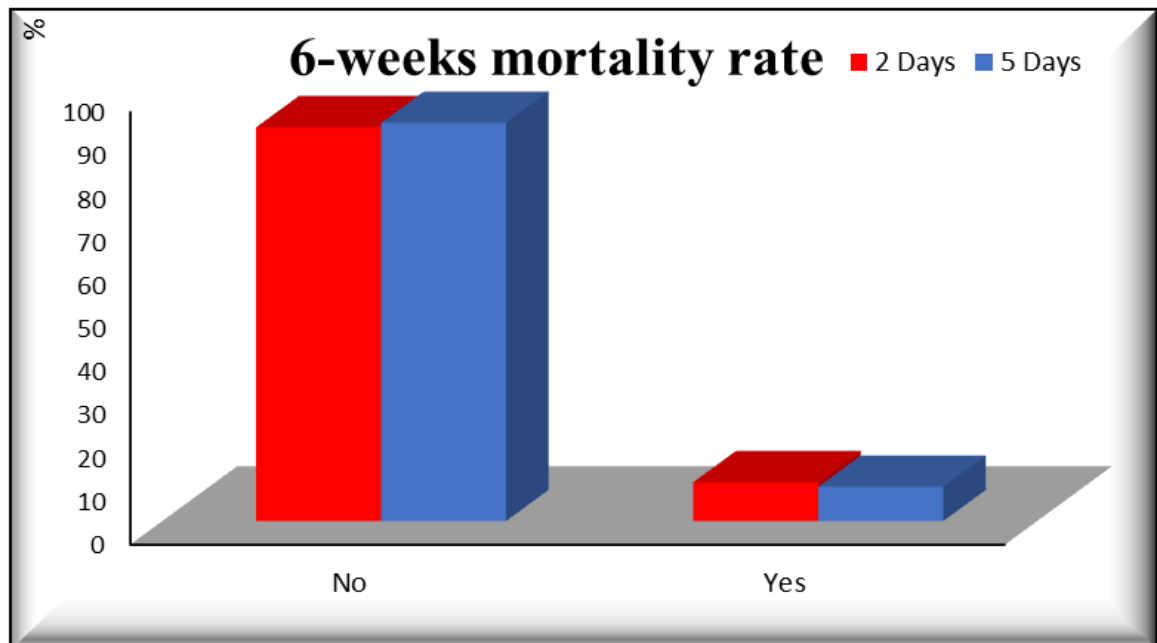**Figure 3.** Six-weeks rebleeding rate

Figure 4. Six-week mortality rate

Our results were near to [5] .who reported that 6-weeks rebleeding rate was 5.8% and 12.1% in cirrhotic patients underwent early (12 hours) endoscopic intervention to control esophageal varices bleeding versus late endoscopy group respectively. A much higher rate of rebleeding was reported by [7] . who evaluated the predictors of 6-weeks rebleeding and mortality following acute variceal bleeding in individuals with cirrhosis and demonstrated that 6-weeks rebleeding rate was 30%. This difference from our study could be attributed to the inclusion of hepatocellular carcinoma, renal impairment and HIV patients in their study. In our work, 6-weeks mortality rate were 8.99% and 7.95% in the 2 days and 5 days octreotide groups respectively. This agreed with [5] . who reported that 6-weeks mortality rate was 12.9 % in cirrhotic patients received combination of octreotide infusion and endoscopic intervention to control variceal bleeding. On the other hand, it disagreed with [8] . who reported that 6-weeks mortality rate was 26.9% in cirrhotic patients with variceal bleeding. This could be explained by the modality used to control variceal bleeding was injection sclerotherapy with or without octreotide and difference in regimen of octreotide (dose and duration).

4. Conclusions

A 2-day treatment of octreotide is equally beneficial as a 5-day treatment in avoiding rebleeding for 5 days in cirrhotic individuals with bleeding varices of the esophagus, after the bleeding was successfully controlled with endoscopic intervention. The work received approval by Ethics Committee of Faculty of Medicine, Tanta University. Ethical committee Number 33089 / 04 / 19 and registered on ClinicalTrials.gov, Identifier: NCT05199038.

Financial support and sponsorship

Nil.

Conflict of Interest

Nil.

References

[1] D.E. Kaplan, C. Ripoll, M. Thiele, B.E. Fortune, D.A. Simonetto, G. Garcia-Tsao, J. Bosch. (2024). AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 79 (5) 1180-1211.

[2] R. De Franchis, J. Bosch, G. Garcia-Tsao, T. Reiberger, C. Ripoll, J.G. Abraldes, H. Yoshiji. (2022). Baveno VII–renewing consensus in portal hypertension. Journal of hepatology. 76 (4) 959-974.

[3] G. Garcia-Tsao, J.G. Abraldes, N.E. Rich, V.W.S. Wong. (2023). AGA clinical practice update on the use of vasoactive drugs and intravenous albumin in cirrhosis: expert review. Gastroenterology.

[4] Sealed Envelope Ltd. (2019). Create a blocked randomisation list.

[5] G. Esmat, I.M. Hamza, B.E. Abbas. (2014). Outcome of patients undergoing early versus late endoscopic intervention for acute oesophageal variceal bleeding at Air Force Hospital, Egypt. A population based cohort study. Open Journal of Gastroenterology, 2014.

[6] S. Rengasamy, S.M. Ali, S.C. Sistla, C.P. Lakshmi, K.T.H. Kumar. (2015). Comparison of 2 days versus 5 days of octreotide infusion along with endoscopic therapy in preventing early rebleed from esophageal varices: a randomized clinical study. European journal of gastroenterology & hepatology. 27 (4) 386-392.

[7] J. Altamirano, L. Zapata, S. Augustin, L. Muntaner, A. González-Angulo, A.L. Ortiz, J. Genescà. (2009). Predicting 6-week mortality after acute variceal bleeding: role of Classification and Regression Tree analysis. Annals of Hepatology. 8 (4) 308-315.

[8] M. Primignani, B. Andreoni, L. Carpinelli, A. Capria, G. Rocchi, I. Lorenzini, T.N.I.E. Club. (1995). Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: a randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 21 (5) 1322-1336.