Primary Prophylaxis of Cardio-fundal Varices: A Comparative Study

Mona Mahmoud El- Khwanky, Ahmed F. Omar , Amira Mohamad Soliman, Sahar A. Elnimr, Mohamed M Refaey,Ahmed M. El-Gebaly
Department of Tropical Medicine, Faculty of Medicine, Zagazig University, Egypt.

Corresponding Author Mona Mahmoud El-khwanky

Mobile: +201273799703

E mail: mymelkhwanky85@gmail.com

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Background and study aims: Gastric varices (GV) are less frequent than esophageal varices (EV) and have a lower risk of bleeding. However, they are more prone to serious bleeding, often requiring more blood transfusions, and have a higher mortality rate. Our study assessed the comparative effectiveness of three modalities: endoscopic cyanoacrylate injection, non-selective beta-blockade and no primary prophylactic treatment.

Patients and Method: Forty-eight cirrhotic patients with cardio-fundal varices were classified into three groups of16 patients each: group I: cyanoacrylate injected patients, group II: propranolol treated patients and group III: untreated patients. Upper gastrointestinal endoscopy was performed to establish the variceal status and repeated at 6-month intervals for 24 months to record of size of GV, appearance of EV, portal hypertensive Gastropathy (PHG) and occurrence of gastric variceal bleeding. Mortality rate was also recorded.

Results: Gastric variceal bleeding and mortality rates in group I, II and III were 6.2% and 18.8%; 31.2% and 6.2%, 6.2% and 12.5% (p= 0.194 and p= 0.761 respectively). All patients in group I had obliterated GV. The percentage of patients with large GV increased from 18.8 to 37.5% (p=0.055) in group II and from 25 to 56.2% (p=0.002) in group III. During follow up, EV appeared in 25% of patients in group I, 6%in group II and12% in group III (p=0.509).

Conclusion: No significant difference in occurrence of gastric variceal bleeding or mortality rates among the three groups managed with cyanoacrylate injection, propranolol administration and observation without treatment .

INTRODUCTION

Variceal bleeding is a serious complication of cirrhosis and portal hypertension; with a high mortality rate of about 20% **[1]**. Gastric varices (GV) are less common than esophageal varices (EV) found in 20% of patients with portal hypertension **[2]**.

The risk of bleeding of GV is lower than EV, but they are more prone to serious bleeding leading to more blood transfusions and a higher mortality **[3]**. The incidence of gastric varices in cirrhotic patients who have not had prior bleeding is 4% **[2]**.

GV are classified as isolated gastric varices (IGVs) and gastroesophageal varices (GOVs), where gastric varices are contiguous with esophageal varices. Isolated gastric varices (IGVs) are classified into IGVs in the fundus (IGV1) and IGVs in the gastric body, pylorus or antrum (IGV2). Gastroesophageal varices (GOVs) are classified into GOV1 (GOVs along the lesser curve of the stomach) and GOV2 (GOVs along the fundus). The term "cardio-fundal varices"commonly refers to GOV2 and IGV1 **[4]**.

The commonest type of gastric varicesis GOV1 (70%) followed by GOV2 (21%), IGV1 (7%) and IGV2 (2%). Isolated gastric varices have the highest incidence of bleeding (78%) followed by GOV2 (55%).The incidence of bleeding from GOV1 and IGV2 bleeding is 10% **[5]**.

Pharmacological or endoscopic treatment for primary prophylaxis of gastric variceal bleeding has not been tested in appropriate studies and recommendations are based only on

guidelines for the management of esophageal varices **[6]**.

PATIENTS AND METHODS

I- Patients

This study was conducted among 48 cirrhotic subjects with endoscopically proven Cardio-fundal varices at Endoscopy Unit, Tropical Medicine Department, Zagazig University Hospitals, Egypt. Subjects were classified into three groups of 16 patients each: group I, cyanoacrylate injected patients, group II, propranolol treated; and group III, who had no treatment. They were followed-up 6-monthly for two years.

Inclusion criteria:

Cirrhotic patients with endoscopically visualized cardio-fundal varices with no history of previous bleed. For subjects with GOV2, esophageal varices were eradicated prior to being included in the study. Diagnosis of cirrhosis was established by clinical, lab and sonographic criteria.

Exclusion criteria:

Subjects with coexistent cardiac or respiratory disease, previous or current bleeding from GV, previous endoscopic gastric variceal injection, non-cirrhotic portal hypertension, contra-indication to beta-blocker use or on a beta-blocker, portal vein thrombosis or hepatocellular carcinoma were excluded.

II- Methods:

Study subjects underwent full clinical history taking, thorough clinical examination, laboratory investigations (full blood count, liver and kidney function tests, coagulation profile i.e. PT and INR, calculation of Child Pugh classification, pelvic-abdominal ultrasound(for diagnosis of cirrhosis, evaluation of diameter of portal vein and its patency, splenomegaly, collaterals, and ascites) and esophago-gastroduodenoscopy to determine type of cardiofundal varices (GOV2 or IGV1), size of GV: small (< 5 mm), moderate (5-10 mm) and large varices (> 5 mm), appearance of EV, presence of portal hypertensive gastropathy (PHG) and occurrence of gastric variceal bleeding.

Cyanoacrylate injection: Cyanoacrylate was injected into the varix lumen in 1-1.5 mL aliquots using normal saline or sterile water (approximately 0.8-1.0 mL, equal to the dead space) to flush Cyanoacrylate into the varix. As the injecting needle was withdrawn from varix, a steady stream of the flush solution is directed at the puncture site. Additional Cyanoacrylate was injected until the varix was‘‘ hard ’’to palpate **[7].**

Non selective beta-blockers (NSBBs): The prescribed dose of propranolol was 20–40 mg twice to reach a resting heart rate of 55–60 beats per minute while keeping systolic blood pressure above 90 mmHg **[8].**

Follow up:

Upper GIT endoscopy was done to determine the status of varices at baseline and repeated each 6 months or during bleeding for a total follow-up of two years. Key study end points were occurrence of gastric variceal bleeding, or death.

Statistical analysis:

Data were validated and analyzed using SPSS. Data was expressed as mean±SD for quantitative parametric variables and median for non-parametric variables. Categorical variables were expressed as frequency and percentage. ANOVA, Paired Samples T, Pearson Chi-Square tests were used. P value < 0.05 was the cut-off for statistical significance.

RESULTS

This study was done on 48 patients; 31 males and 17 females. Their ages ranged from 48 to73 years. More than one third (35.4%) of patients were Child A, 50% Child B and 14.6% Child C without significant difference among patients' groups (Table 1).

The frequency of IGV1 was 27.1% and GOV2 was 72.9% (Table 2).There was no significant difference in GV grades among pre-treatment groups. The GV grades, small, medium and large represented 35.4%, 39.6% and 25% of all patients respectively. Findings among post-treatment groups were as follows: in cyanoacrylate group, all patients had obliterated GV, while in β-blocker treated group, there was an increase from 3 to 6 cases of patients with large varices and a non- significant decrease in number of cases with small and medium grades. In the untreated group, there was an increase in number of patients with large GV from 4 to 9 (56.2%) (Table3).

There was no difference in grades of PHG among patients' groups before and after treatment. In cyanoacrylate treated group there was a significant increase in PHG from 37.5% (6/16) to 56.25% (9/16). In β-blocker treated patients, despite a decrease in PHG grade II from 25% (4/16)to 6.2% (1/16) after treatment, the overall number did not show any significant decrease. In the untreated group, there was no significant change in numbers of patients with PHG (Figure 1).

There was no significant change in the condition of esophageal varices after treatment among all groups. In some patients, new appearance of EV occurred after treatment (EV appeared in one patient each in the cyanoacrylate injected group and untreated group) and in others reappearance of previously obliterated EV occurred (three in cyanoacrylate injected, one in each of non-selective B-blocker treated and untreated group) (Table 4). Gastric variceal bleeding occurred during the course of follow up in 6.2% within group I, 18.8% in group II and 31.2% in group III without any significant difference(table 5, 6). There was no remarkable difference in numbers of mortality among patients' group: 6.2% in group I, 6.2% in group II and 12.5% in group III (Table 7).

Table (1): Child Pugh classification among patients' groups.

			Group			X^{2*}	p
			Cyanoacrylate injected (n=16)	B-blocker treated (n=16)	Untreated (n=16)		
Child class	A	n	7	4	6	1.859	0.762
		%	43.8	25	37.5		
	B	n	7	10	7		
		%	43.8	62.5	43.8		
	C	n	2	2	3		
		%	12.5	12.5	18.8		

* X^2 = Pearson Chi-Square test

Table (2): Types of gastric varices among patients' groups.

			Groups			Total	X^{2*}	*P*
			Cyanoacrylate injected	B-blocker treated	Untreated			
GV type	IGV1	n	6	4	3	13	1.477	0.478
		%	37.5	25	18.8	27.1		
	GOV2	n	10	12	13	35		
		%	62.5	75	81.2	72.9		

* X^2 = Pearson Chi-Square test
- IGV1 (Isolated gastric varices type 1)
- GOV2 (Gastro-esophageal varices type 2)

Table (3): Distribution of gastric varices' grades among patients' groups (pre-and post-treatment).

Treatment			Groups						X^{2*}	*P*
			Cyanoacrylate injected		B-blocker treated		Untreated			
			Pre	Post	Pre	Post	Pre	Post		
GV size	Small	n	5	0	6	4	6	3	Among pre-treatment groups	
		%	31.25	0	37.5	25	37.5	18.8		
	Medium	n	6	0	7	6	6	4	0.723	0.948
		%	37.5	0	43.8	37.5	37.5	25		
	Large	n	5	0	3	6	4	9	Among post-treatment groups	
		%	31.25	0	18.8	37.5	25.0	56.2		
	Obliterated	n	--	16	--	0	--	0	49.71	0.000
		%	--	100	--	0	--	0		
Paired Samples T Test										
	t		9.798		-2.076		-3.873			
	p		0.000		0.055		0.002			

* X^2= Pearson Chi-Square test.

Table (4): The condition of esophageal varices (EV) in patients' groups pre- and post- treatment.

Treatment			Groups						X^{2*}	*P*
			Cyanoacrylate injected		B-blocker treated		Untreated			
			Pre	Post	Pre	Post	Pre	Post		
EV	No	n	6	5	4	4	3	2	Pre-	
		%	37.5	31.2	25	25	18.8	12.5	1.477	0.478
	Obliterated	n	10	7	12	11	13	12	Post-	
		%	62.5	43.8	75	68.8	81.2	75.0	5.273	0.509
	t		-2.076		-1.000		-1.379			
	p		0.055		0.333		0.188			

*X^2 = Pearson Chi-Square test.

Table (5): Number of patients that bleed from their GV during the course of follow up in patients' groups.

			Groups				X^{2*}	*P*
			Cyanoacrylate injected	B-blocker treated	Untreated	Total		
Bleeding from GV during the course of treatment	Yes	n	1	3	5	9	3.282	0.194
		%	6.2	18.8	31.2	18.8		
	No	n	15	13	11	39		
		%	93.8	81.2	68.8	81.2		

* X^2= Pearson Chi-Square test.

Table (6): Time of bleeding from GV during the course of follow up in patients' groups.

	GV bleeding		
	cyanoacrylate	B-blocker	untreated
6^{th} month follow up	0	0	1
12^{th} month follow up	0	1	1
18^{th} month follow up	0	0	1
24^{th} month follow up	1	2	2

Table (7): Mortality among patients' group.

			Groups				X^{2*}	*P*
			Cyanoacrylate injected	B-blocker treated	Untreated	Total		
Mortality rate	Died	n	1	1	2	4	0.545	0.761
		%	6.2	6.2	12.5	8.3		
	Alive	n	15	15	14	43		
		%	93.8	93.8	87.5	91.7		

* X^2= Pearson Chi-Square test.

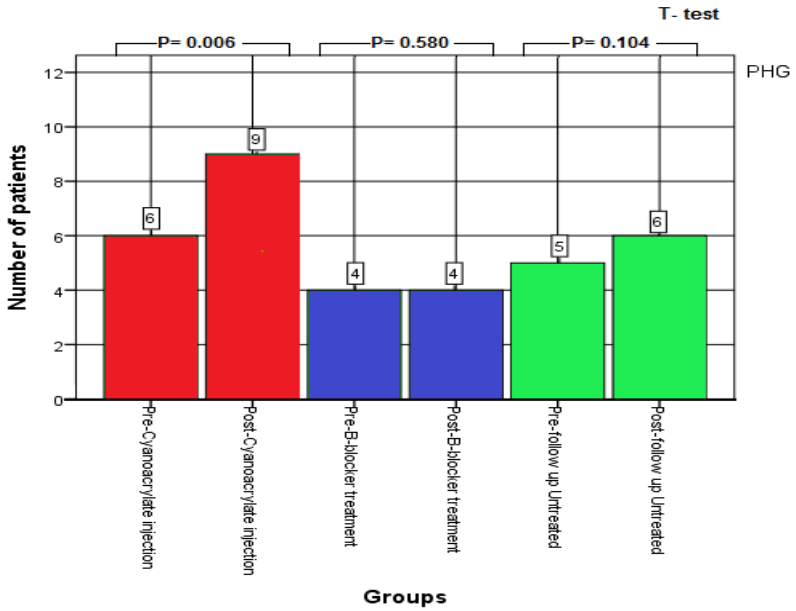

Figure (1): Changes in number of patients with PHG before and after treatment.

DISCUSSION

Our results showed insignificant changes in grades or numbers of patients with (PHG) among all patients' groups before and after treatment. The number of patients with PHG increased significantly in cyanoacrylate injected patients (from 37.5% to 56.25%). Mishraet al. (2011) also compared the efficacy of endoscopic cyanoacrylate injection, non-selective beta-blockers, and no treatment for primary prophylaxis of cardio-fundal varices. They studied 89 patients and reported that the appearance or worsening of PHG was not significant among groups (7/30 '23%', 2/29 '7%' and 3/30 '10%' for groups I, II and III respectively) **[10]**.

We found no significant difference in GV grades among study groups before treatment. After treatment, all patients in cyanoacrylate injected group obtained complete obliteration of their GV. An increase in the number of patients with large varices and decrease in small and medium varices occurred significantly in untreated group and insignificantly in propranolol treated group.

Regarding cyanoacrylate injected group, the same result was reported by Mishra et al. (2011) but Salma et al. (2020) reported complete obliteration only in 42.8% with the remaining patients showing a decrease in their GV size **[11]**. This difference between studies may be due to the period of follow-up, which was 24 months in our study, 34 months in Mishra study and 6 months in Salma study. Some patients need over one session of cyanoacrylate injection to obtain complete obturation of their GV **[12]**. As regards β-blocker treated and untreated groups, both Mishra and Salma reported a significant increase in GV size.

Our research showed that the difference in frequency of GV bleeding during the course of treatment and follow-up in all groups of patients was insignificant. Mishra et al. (2011) reported 10%, 38% and 53% and Salma et al. (2020) reported 6.67%, 20% and 36.67% in the three groups, respectively with significant differences. Patients in Mishra et al had large sized gastric

varices (>10mm for all patients, median=20 mm), long follow-up (34 month), and a higher proportion in Child C class.

Mishra et al. (2011) assessed hepatic venous pressure gradient (HVPG) in the three groups prior to and after treatment and recorded a significant decrease in HVPG with propranolol and an increase in the other groups. Despite the HVPG, response to non-selective beta-blockers (NSBB) has been shown to predict both bleeding and the evolution of esophageal varices **[13]**. This is not the case in gastric varices as 40% of responders and 37% of non-responders bled on follow-up. This implies that GV bleeding depends not just on the HVPG, but also on the tension of the wall and the size of the varices **[9]**. It also means that gastric varices will bleed at lower pressures compared to esophageal varices, meaning that a reduction in portal pressure would have less effect on the risk of bleeding, or that a higher degree of pressure reduction is necessary to protect against bleeding **[14]**. In this context, because Carvedilol has been shown to be more effective than propranolol in reduction of HVPG and bleeding rates as primary prophylaxis of EV **[15]** this drug is worth of research in cases of GV.

There was no significant change in the condition of esophageal varices after treatment among patients 'groups. The new appearance or reappearance of previously obliterated EV was as follows: 4/16 (25%) in group (I), 1/16 (6%) in group (II) and 2/16 (12%) in group (III). This is consistent with Mishra et al who reported 23% in group I, and 10% in group II and III without significant differences.

El-medammes et al. (2014) found that sclerotherapy of esophageal varices was associated with development of gastric varices in 10% of patients **[16]**. On the other hand, Choi et al. (2008) concluded that Balloon occluded retrograde transvenous obliteration(B-RTO) used for mangement of gastric variceal bleeding increased the bleeding rate of coexisting EV in the long term due to obliteration of a major collateral shunt and subsequent increase in portal blood flow via the EV **[17]**. This may explain the greater frequency of EV in cyanoacrylate injected group in our study and that of Mishra in spite of absence of significance.

This study found no significant difference in mortality rates among patient groups. The mortality rate was 6.2% in group I and II and 12.5% in group III. It is concordant with Mishraet al where the mortality was significantly lower in group I (7%) compared to group III (26%) but without significant difference between group I vs. group II. Additionally, Kang and colleagues managed 27 patients (Child C) with high-risk fundal varices by endoscopic injection with histoacryl for primary prophylaxis and reported 4 deaths (14.8%) after 6 months of follow-up **[12]**. It is difficult to persuade patients or physicians to accept prophylactic cyanoacrylate if it has not been shown to be more effective than propranolol in improving survival **[18]**.

Glue injection requires good experience which is not consistently available, and the low complication rate in the available studies indicates the high skill of endoscopists who conducted these studies, which is not commonly reproducible **[18]**. Thrombin injection is encouraging and could be a more appealing choice due to ease of use and lack of complications compared to cyanoacrylate **[19]**, but it has yet to be tested in a controlled clinical trial **[18]**.

The use of non-selective beta-blockers (NSBB) as primary prophylaxis and the avoidance of cyanoacrylate injections are suggested by some experts because they consider the available studies to be very descriptive and not sufficient evidence to generalise their findings **[20]**. In addition, the efficacy difference between NSBB and cyanoacrylate injection may be narrowed by data indicating that Carvedilol is more efficient in reducing HVPG **[6]**.

CONCLUSION

Primary prophylaxis of gastric varices is recommended because of the high risk of serious bleeding and its attendant complications. This study did not find difference in occurrence of gastric variceal bleeding or mortality rates among subjects managed with cyanoacrylate injection, propranolol administration and observation without treatment as primary prophylactic measures against gastric variceal bleeding. The number of patients in this study is too small to be generalizable. Therefore, the need of multi-center randomized controlled studies to determine which option is the best in primary prophylaxis of gastric variceal bleeding cannot be overemphasized.

Recommendation: Gastric varices shouldn't be left without treatment as its size enlarges with the time that increases the susceptibility to bleeding. Our study recommended that cyanoacrylate injected was a better outcome than BB and untreated group, as cyanoacrylate injection was the least bleeding and mortality rate, but without a significant difference.

Ethical considrations: Informed consent had been be taken from each patient before inclusion in this study. In addition to an approval from the official department, ethical committee in the faculty and IRB had been obtained.

Conflict of interest: Nothing to declare.

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