ORIGINAL ARTICLE

SAFETY AND EFFICACY OF N-BUTYL-2-CYANOACRYLATE FOR MANAGEMENT OF GASTRIC VARICES

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Background: Gastric varices (GVs) bleed less frequently than oesophageal varices. Gastric variceal bleeding tends to be severe with higher mortality and re-bleed frequently after spontaneous haemostasis. This study evaluated the safety and efficacy of N-Butyl-2-Cyanoacrylate for the management of gastric varices in patients presenting to tertiary care setting. **Methods:** This descriptive case study was performed at Department of Gastroenterology and Hepatology, Hayatabad Medical Complex, Peshawar between Jan and July 2022. Seventy-three patients of either gender were included in the study. Screening and interventional endoscopy were done and patient were observed for efficacy and safety of N-Butyl-2-Cyanoacrylate injection. Data was analysed using SPSS-22. **Results:** The mean age and BMI of the patients were 54.96±2.64 years and 28.98±246 Kg/m^2 respectively. There were 75.78% male and 24.21% female (M:F=31:1) patients. The aetiological cause of gastric varices was Hepatitis-B virus in 62.10%, alcohol in 23.15% and other causes in 14.73% patients. Child Pugh Class was A in 37.89% patients, B in 50.52% and C in 11.57% patients. Adequate haemostasis was achieved in 95.78% patients and re-bleeding was observed in 30.52% patients. Fever was recorded in 5.26% patients, abdominal pain in 3.15% and diarrhoea in 1.05%. Spontaneous bacterial peritonitis was not reported in any case (0.0%). **Conclusion:** N-Butyl-2-Cyanoacrylate is efficacious and safe for the management of gastric varices.

Keywords: N-Butyl-2-Cyanoacrylate, Gastric varices, efficacy, Peshawar, Pakistan

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INTRODUCTION

Dilated sub-mucosal veins in the stomach known as gastric varices (GV) can cause life-threatening upper gastrointestinal bleeding. Patients with portal hypertension or elevated pressure in the portal vein system, which may be a complication of cirrhosis, are most likely to have them. After oesophageal varices (EV), GV are the most frequent cause of upper gastrointestinal (UGI) bleeding in patients with portal hypertension.[1] The gastro-oesophageal (azygous) venous system and the gastro-phrenic venous system are two different types of portosystemic collateral drainage systems that can be used to drain gastric varices that originate at hepatofugal collateral pathways into the systemic vein. Occasionally, localized portal hypertension brought on by splenic vein occlusion results in gastric varices at the hepato-petal collateral pathway. These varices drain through the stomach veins.[2] Gastric varices may also be found in patients with splenic vein thrombosis into which the short gastric veins drain stomach flow. Gastric varices and bleeding are a possible complication of schistosomiasis caused by portal hypertension.[3] Hematemesis, melena, or rectal bleeding are all symptoms that patients with bleeding gastric varices may exhibit. The patients may experience rapid bleeding and may go into shock soon.[4]

Approximately 10–30% of variceal haemorrhage is caused by GV. They have a higher mortality rate and a propensity to bleed more heavily. After spontaneous haemostasis, between 35 and 90% of patients re-bleed. Around 50% of people with liver cirrhosis have gastro-oesophageal varices.[5] Acute upper gastrointestinal bleeding is one of the leading causes of hospitalization worldwide, with an annual incidence of 50–150 episodes per 100,000 people. Acute upper gastrointestinal bleeding is associated with a 10–14% mortality rate.[6] Recent studies reported the incidence of gastric varices due to various causes about 15% in Pakistani population. In 40–50% patients, variceal bleeding stops on its own, but within the first six weeks, the incidence of early re-bleeding varies between 30–40%, and about 40% of all re-bleeding episodes happen within the first five days.[7] The most accepted classification of GV differentiates them into two types, i.e., those caused by portal hypertension (cirrhotic or non-cirrhotic) and those caused by isolated splenic vein thrombosis (SVT). GV caused by portal hypertension is much more common than GV caused by SVT.[8]

Gastric varices bleeding must be controlled or managed using a combination of treatment strategies. Patients with cirrhosis or high portal blood pressure are more likely than patients with SVT to experience gastric variceal bleeding.[9] The bleeding causes significant blood loss, which must be compensated for by blood transfusion to maintain circulation of blood. New endoscopic treatment options and interventional radiological procedures have recently expanded the

therapeutic arsenal for GV.[10] Cyanoacrylate glue therapy, trans-jugular intrahepatic portosystemic shunt (TIPSS), balloon-occluded retrograde transvenous obliteration (BRTO), and devascularisation surgery are all treatment options for bleeding GV.[11]

For gastric variceal obturation, tissue adhesives have been used, such as N-butyl-2-cyanoacrylate (NB2-CY), a monomer that quickly undergoes exothermic polymerization upon contact with the hydroxyl ions present in water. A cyanoacrylate ester known as N-butyl cyanoacrylate (n-BCA, NBCA) is a butyl ester of 2-cyano-2-propenoic acid.[12] It has a sharp, offensive smell and is a clear, colourless liquid. It does not dissolve in water and its primary function is as the foundational element of cyanoacrylate medical glues.[13] Past studies reported higher efficacy and safety for controlling GV using cyanoacrylate but these studies haven't been performed on our local population. The current study's goal was to assess the safety and efficacy of N-butyl-2-octyl-cyanoacrylate in treatment of patients with gastric varices in local population.

PATIENTS AND METHODS

This was a descriptive case studies performed at Department of Gastroenterology and Hepatology, Hayatabad Medical Complex, Peshawar from 21st January to 20th July 2022. Permission and approval of the study were taken from the Hospital Ethics Committee. Sample size was calculated through World Health Organization online sample size calculator using 95% confidence level with anticipated population proportion of 96.9% and absolute precision of 4%. Non-probability consecutive sampling technique was used. Patient of either gender with ages 18–75 years with high risk of gastric varices, i.e., varices of more than 1 Cm size, history of bleeding from gastric varices and those with cirrhosis of Child Turcotte Pugh Score greater than 5 were included in our study. Pregnant and lactating mothers, patients with shock or Grade III/IV hepatic encephalopathy, bleeding secondary to oesophageal varices or portal hypertensive gastropathy and those having sensitivity to N-butyl-2-octyl-cyanoacrylate were excluded from the study. Written informed consent was obtained from the patients.

Screening and interventional endoscopy were done in Gastroenterology Ward, Lady Reading Hospital, Peshawar. Patients were observed for hematemesis and vital record, and full blood count were obtained six hourly for 48 hours. The procedure was performed using a standard forward-viewing video endoscope (Pentax EG 29910). N-Butyl-2-Cyanoacrylate (Histoacryl, B Braun, Germany) was mixed with lipiodol ((Lipiodol Ultra Fluid, Therapex, Canada) in 1:1 ratio and injected into bleeding fundal varices. The volume used was 0.5–4 mL injection, decided according to size of varix. Data was recorded on a pre-designed proforma and analysed on SPSS-22. Numerical variables, i.e., age, BMI and number of patients included were summarized as Mean±SD. Qualitative variables like aetiology of GV, Child Pugh class, re-bleeding, homeostasis, fever, abdominal pain, diarrhoea and SBP were presented as frequency and percentage. Effect modifiers like age, gender, BMI, aetiology of GV and Child Pugh class were controlled by stratification. Post-stratification Chi-square test was applied keeping $p<0.05$ as significant.

RESULTS

There were total 95 patients included in this study. The mean values for numeric variables of the patients who received N-butyl-2-cyanoacrylate are shown in Table-1. The mean values for qualitative variables are shown in Table-2.

The mean BMI of patients who received N-butyl-2-cyanoacrylate for management of gastric varices was 28.98±2.46 Kg/m^2. Out of 95 patients with gastric varices, there were 1 (1.05%) patient of BMI <18.5 Kg/m^2, there were 19 (20.0%) patients of BMI range of 18.5–24.9 Kg/m^2, 51 (53.68%) patients of BMI range of 25–29.9 Kg/m^2 and 24 (25.26%) patients of BMI range of ≥30 Kg/m^2. Stratification of age and gender with respect to efficacy and safety of N-Butyl-2-Cyanoacrylate is shown in Table-3.

Stratification by child Pugh score and aetiology of varices is shown in Table-4.

Table-1: Distribution of patients (n=95)

Variables		Patients (n)	Percentage (%)	Mean±SD
Age Groups (Years)	18–20	2	2.10	54.96±2.64 (Years)
	21–30	4	4.21	
	31–40	7	7.36	
	41–50	17	17.89	
	51–60	36	37.89	
	61–70	20	21.05	
	71–75	9	9.47	
Gender	Male	72	75.78	–
	Female	23	24.21	

Table-2: Qualitative variables distribution (n=95)

	Distribution		Patients (n)	Percentage (%)
Aetiology of gastric varices	Viral		59	62.10
	Alcoholic		22	23.15
	Others		14	14.73
Child Pugh class	A		36	37.89
	B		48	50.52
	C		11	11.57
Efficacy	Haemostasis	Yes	91	95.78
		No	4	4.21
	Re-bleeding	Yes	29	30.52
		No	66	69.47
Safety	Fever	Yes	5	5.26
		No	90	94.73
	Abdominal pain	Yes	3	3.15
		No	92	96.84
	Diarrhoea	Yes	1	1.05
		No	94	98.94
	Spontaneous bacterial peritonitis	Yes	0	0
		No	95	100

Table-3: Stratification of Groups

	Efficacy					Safety								
	Haemostasis (n=95)		Re-bleeding (n=95)			Fever		Abdominal		Diarrhoea		Spontaneous bacterial peritonitis		
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	p*	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	p*
Stratification by Age														
18–20 (n=2)	2 (100.0)	0 (0,0)	0 (0.0)	2 (100.0)		0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (100)	
21–30 (n=4)	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)		0 (0.0)	4 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)	4 (100)	
31–40 (n=7)	7 (100.0)	0 (0.0)	0 (0.0)	7 (100.0)		0 (0.0)	7 (100.0)	0 (0.0)	7 (100.0)	0 (0.0)	7 (100.0)	0 (0.0)	7 (100)	
41–50 (n=17)	16 (94.11)	1 (5.88)	4 (23.52)	13 (76.47)	0.821**	1 (5.88)	16 (94.11)	1 (5.88)	16 (94.11)	1 (5.88)	16 (94.11)	0 (0.0)	17 (100)	0. 630**
51–60 (n=36)	35 (97.23)	1 (2.78)	18 (50.0)	18 (50.0)		3 (8.34)	33 (91.67)	1 (2.78)	35 (97.24)	0 (0.0)	36 (100.0)	0 (0.0)	36 (100)	
61–70 (n=20)	19 (95.0)	1 (5.0)	3 (15.0)	17 (85.0)		1 (5.0)	19 (95.0)	1 (5.0)	19 (95.0)	0 (0.0)	20 (100.0)	0 (0.0)	20 (100)	
71–75 (n=9)	8 (88.89)	1 (11.12)	4 (44.45)	5 (55.56)		0 (0.0)	9 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	9 (100.0)	0 (0.0)	9 (100)	
Total	91 (95.78)	4 (4.21)	29 (30.52)	66 (69.47)		5 (5.26)	90 (94.73)	3 (3.15)	92 (96. 84)	1 (1.05)	94 (98. 94)	0 (0.0)	95 (100)	
Stratification by Gender														
Male (n=72)	70 (97.23)	2 (2.78)	21(29.16)	51 (70.83)	0. 319**	4 (5.56)	68 (94.45)	3 (4. 16)	69 (95.83)	1 (1.38)	71 (98.61)	0 (0.0)	72 (100)	0. 267**
Female (n=23)	21 (91.30)	2 (8.69)	8 (34.78)	15 (65.21)		1 (4.34)	22 (95.65)	0 (0. 0)	23 (100.0)	0 (0.0)	23 (100.0)	0 (0.0)	23 (100)	
Total	91 (95.78)	4 (4.21)	29 (30.52)	66 (69.47)		5 (5.26)	90 (94.73)	3 (3.15)	92 (96.84)	1 (1.05)	94 (98.94)	0 (0.0)	95 (100)	

Table-4: Stratification of Groups

	Efficacy					Safety								
	Haemostasis (n=95)		Re-bleeding (n=95)			Fever		Abdominal		Diarrhoea		Spontaneous bacterial peritonitis		
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	p*	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	p*
Stratification by Child Pugh Class														
A (n=36)	35 (97.23)	1 (2.78)	9 (25.0)	27 (75.0)		2 (5.56)	34 (94.45)	1 (2.78)	35 (97.23)	1 (2.78)	35 (97.23)	0 (0.0)	36 (100)	
B (n=48)	46 (95.83)	2 (4.16)	18 (37.5)	30 (62.5)	0.214**	3 (6.25)	45 (93.75)	2 (4.16)	46 (95.83)	0 (0.0)	48 (100.0)	0 (0.0)	48 (100)	**0 . 577 * ***
C (n=11)	10 (90.90)	1 (9.09)	2 (18.18)	9 (81.81)		1 (9.09)	10 (90.90)	0 (0.0)	11 (100.0)	0 (0.0)	11 (100.0)	0 (0.0)	11 (100)	
Total	91 (95.78)	4 (4.21)	29 (30.52)	66 (69.47)		5 (5.26)	90 (94.73)	3 (3.15)	92 (96.84)	1 (1.05)	94 (98.94)	0 (0.0)	95 (100)	
Stratification by Aetiology of Varices														
Viral (n=59)	57 (96.61)	2 (3.38)	23 (38.98)	36 (61.01)		2 (3.38)	57 (96.61)	1 (1.69)	58 (98.30)	1 (1.69)	58 (98.30)	0 (0.0)	59 (100)	
Alcoholic (n=22)	21 (95.45)	1 (4.54)	6 (27.27)	16 (72.72)	0. 982**	3 (13.63)	19 (86.36)	2 (9.09)	20 (90.90)	0 (0.0)	22 (100.0)	0 (0.0)	22 (100)	0.743**
Others (n=14)	14 (100.0)	0 (0.0)	0 (0.0)	14 (100.0)		1 (7.14)	13 (92.58)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100.0)	0 (0.0)	14 (100)	
Total	91 (95.78)	4 (4.21)	29 (30.52)	66 (69.47)		5 (5.26)	90 (94.73)	3 (3.15)	92 (96.84)	1 (1.05)	94 (98.94)	0 (0.0)	95 (100)	

DISCUSSION

Gastric varices (GVs) are known for massive bleeding and are frequently challenging to treat using standard methods. Approximately half of all cirrhosis patients have gastric varices. It usually happens after oesophageal varices and is the most frequent cause of upper gastrointestinal tract bleeding with high portal blood pressure.[14] Knowledge of the pathophysiology and treatment options for patients with gastric varices has significantly changed over the past 20 years. The majority of GV patients in the United States have underlying portal hypertension rather than splenic vein thrombosis, but ruling out the latter is still a crucial first step in the assessment.[15] Varices that develop in the stomach's fundus are particularly troublesome. Fundal varices can sometimes appear as polypoid masses occasionally resembling a cluster of grapes.[16] In the current study on 95 patients, we determined the safety and efficacy of N-Butyl-2-Cyanoacrylate for the management of gastric varices in the patients presenting to tertiary care setting.

In a study by Lizardo-Sanchez L *et al*[17], there were 9 (56%) males and 7 (44%) females, while in another study conducted by Jun CH *et al*[18], there were 379 males (83.3%) and 76 females (16.7%). In a study of Mosli MH *et al*[19], the majority of patients were males 79.3% (95% CI, 63.6–95%). In the current study, there were 75.78% male and 24.21% female patients (M:F ratio 31:1). It was reported that immediate haemostasis was achieved in 93% of patients with GV and no complication was observed following 2-octyl-cyanoacrylate injection.

A study by Jun CH *et al*[18], evaluated the efficacy and safety of N-Butyl-2-Cyanoacrylate for treatment of GV and they found that haemostasis achieved initially in 96.9% (441/455) of patients; re-bleeding occurred in 35.2% (160/455), and the bleeding-related death rate was 6.8% (31/455) during follow-up. Complications recorded following NB2-CYA therapy were included fever (6.8%), abdominal pain (3.7%), diarrhoea (1.3%), spontaneous bacterial peritonitis (0.7%), bacteremia (0.4%), and embolism (0.2%).[18] In the current study, it was found that majority of patients who achieved adequate haemostasis (100%) were in younger age groups, i.e., 18–20, 21–30 and 31–40 years, followed by older age groups, i.e., 51–60, and 61–70 years age groups, i.e., 97.23% and 95.0% respectively. Lower number of patients who achieved haemostasis was found in older age group (71–75 years). Re-bleeding was not observed in younger age groups however it was higher in middle age groups, i.e., 51–60 years followed by older age groups, i.e., 71–75 years (44.45%). Efficacy of N-Butyl-2-Cyanoacrylate for the management of gastric varices was observed more in younger age groups in our study but results were statistically not significant.

The safety with age was also stratified and found that majority of patients with fever (8.34%), abdominal pain (5.88%) and diarrhoea (5.88%) were observed in middle age group (51–60 years and were not observed in younger and older age groups. However, spontaneous bacterial peritonitis was not observed in any patient. On the other hand, safety of N-Butyl-2-Cyanoacrylate for the management of gastric varices was observed more in younger and older age

groups and less in middle age groups. However, the results were not statistically significant.

The safety of N-Butyl-2-Cyanoacrylate with effect gender was also compared and found that majority of patients with fever (5.56%) were males followed by females (4.34%). All patients with abdominal pain (4.16%) were male. All patients with diarrhoea (1.38%) were male. Spontaneous bacterial peritonitis was not observed in any patient. Safety of N-Butyl-2-Cyanoacrylate for the management of gastric varices was observed more in females and less in males, but the results were not statistically significant. On the other hand, safety and efficacy of N-Butyl-2-Cyanoacrylate for the management of gastric varices was found more in Child Pugh class A and less in class B in our study but results were statistically not significant. The safety and efficacy of N-Butyl-2-Cyanoacrylate for the management of gastric varices was found more in patients who had gastric varices aetiology other than virus and alcohol but results were statistically not significant.

This was a single centred study carried out at a single tertiary facility. A multicentre randomized controlled trial ought to be carried out to see the potential clinical effects of cyanoacrylate.

CONCLUSION

N-Butyl-2-Cyanoacrylate is efficacious and safe for the management of gastric varices. However, large, multicentered study is required to generalize the results in local population.

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