Gastric Varices in Cirrhosis vs. Extrahepatic Portal Venous Obstruction and Response to Endoscopic N-butyl-2-cyanoacrylate Injection

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Background: Gastric varices (GV) are found in patients with portal hypertension. Incidence of bleeding from GV is relatively low, but is severe, and associated with higher mortality. **Aims and objectives:** To compare the types of GV in cirrhosis vs. extrahepatic portal venous obstruction (EHPVO) and the results of endoscopic N-butyl-2-cyanoacrylate (NBC, glue) injection. **Methods:** Four hundred and fifty-four patients undergone glue injection of GV for primary prophylaxis or control of bleeding for first episode of bleeding from GV between August 2010 and August 2015 were analyzed. **Results:** Of 454 patients, 64% ($n = 292$) were cirrhotics and 36% ($n = 162$) had EHPVO. Types of GV were GOV1 in 16.4% ($n = 48$) of cirrhotics vs. 7.4% ($n = 12$) of EHPVO, GOV2 in 76.7% ($n = 224$) of cirrhotics vs. 53.1% ($n = 86$) of EHPVO, Isolated gastric Varices (IGV1) in 39.5% ($n = 64$) of patients with EHPVO vs. 6.8% ($n = 20$) cirrhotics. The patients were treated with NBC injections. The mean volume of glue injected was 2.89 ± 1.59 ml over a median of 1 session (range: 1–7). The total volume of glue required was lower in cirrhotics (2.44 ± 1.17 ml vs. 3.69 ± 1.91 ml, $P < 0.05$) than in EHPVO patients. One hundred and seventeen (40.1%) of cirrhotics required >1 sessions of glue injection as compared to 102 (63%) of EHPVO patients. Over mean follow up of 14.7 ± 6.46 months, rebleeding (10% vs. 13%) was similar in patients with cirrhosis and EHPVO and mortality (15.4% vs. 2.5%) was higher in cirrhotics than EHPVO. **Conclusion:** In patients with bleeding from GV, GOV2 are more common in cirrhotics and IGV1 in patients with EHPVO. Patients with EHPVO required higher total volume of glue and more glue sessions for GV obturation. (J CLIN EXP HEPATOL 2017;7:97–101)

Gastric varices (GV) occur in 18–70% of patients with portal hypertension (PHT) and are responsible for 10–15% of all variceal bleeding.^{1–4} They may develop in the setting of either generalized or segmental (sinistral or left sided) PHT.⁵ Although the incidence of bleeding from GV is relatively low (10–36%), the prognosis of gastric variceal hemorrhage is poorer than esophageal variceal bleeding. The bleeding tends to be more severe, to require more blood transfusion, and to have a higher mortality rate than esophageal variceal bleeding.^{6–8} Mortality associated with a first variceal bleed appears to have improved in recent years but remains as high as 20% within 6 week of the index bleed.^{6,7} GV have a high rate of rebleeding (38–89%).^{9–11} Endoscopic injection using N-butyl-2-cyanoacrylate (NBC, glue) for the treatment of GV was first reported by Soehendra et al.,¹² in 1986.

Current evidence favors the use of NBC as the first-line management option both for acute bleed and for secondary prophylactic eradication of GV.⁵ In the present study we retrospectively analyzed the results of endoscopic NBC injection in 454 cases of GV and the rate of rebleeding in the setting of extrahepatic portal venous obstruction (EHPVO) and cirrhosis of liver.

METHODS

Four hundred and fifty-four patients were retrospectively analyzed who presented with PHT and had undergone glue injection of GV for primary prophylaxis or control of bleeding in patients having first episode of bleeding from GV between August 2010 and August 2015. The diagnosis of PHT was suspected clinically and confirmed by endoscopy. The etiology of the PHT was established by clinical, biochemical, and radiologic parameters, as caused by cirrhosis or EHPVO.

GV were classified according to Sarin's classification.¹ The size of GV was classified according to the system suggested by Hashizume et al.¹³ as Form 1 (F1), tortuous winding varices; F2, nodular shaped varices; F3, tumorous huge varices.

Acute Gastric Varices Hemorrhage (GVH) was defined as GVH less than 24 h between its clinical presentation and endoscopic treatment. Active bleeding defined by the

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Abbreviations: EHPVO: extrahepatic portal venous obstruction; GV: gastric varices; NBC: N-butyl-2-cyanoacrylate; PHT: portal hypertension; TIPS: transjugular intrahepatic portosystemic shunt

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endoscopic findings showing active spurting or oozing of blood from GV. Rebleeding was defined as new onset of hematemesis, coffee-ground vomitus, hematochezia, or melena, with an increasing pulse rate over 100 beats/min and decreasing blood pressure below 90 mmHg after a 24-h period of stable vital signs and hemoglobin after endoscopic treatment. We defined successful hemostasis as stable vital signs, no drop in hemoglobin >2 g/dl and no rebleeding after NBC injection. We defined treatment failure as failure to control acute bleeding after one attempt with the endoscopic methods. GV obturation was defined as firm non-collapsible varices on probing with an injector during endoscopy.

Technique of Variceal Obliteration

All patients with recent or active bleed from GV were injected with glue. Forward viewing video endoscopes (Olympus 180JKV) were used in all the cases. Endoscopic injector with a 21-gauge needle was used. Undiluted NBC was injected intravariceally into the GV after which 2 ml of normal saline was injected to deliver the entire glue from the injector into the varix. Each varix was injected with 1–2 ml of glue depending on the size of the varix. Each time no more than 2 ml of glue was injected into one varix. After the injection, the needle was immediately withdrawn. The endoscope was then taken out with the injector inside. The injector was cut from the proximal end, and it was withdrawn from the tip of the endoscope to prevent blockage of channel by the glue. Relook endoscopy was performed in the same session. Obturation of GV was assessed by probing the injected varices with the injector for firmness. If the varices remained soft, the injection was repeated to achieve complete obliteration. The maximum amount of NBC was 6 ml in 1 session and 2 ml per varix. Repeat endoscopy was performed after 2 weeks for treating remaining GV. Patients underwent primary prophylaxis by using NBC injection if they had large bullous GV. Informed consent was obtained from all the patients.

Follow-up

Monitoring was done for complications like chest pain, shortness of breath, hypoxia, abdominal pain, fever, cough, and rebleeding. Surveillance endoscopies were performed at 3-month intervals to monitor for recurrence of GV.

Statistical Analysis

Each continuous variable between the two treatment groups was expressed as mean $\pm$ SD and analyzed with the Mann-Whitney nonparametric test. Categorical data were examined using the chi-square test. A P value <0.05 was considered statistically significant. All analyses were performed by using the Statistical Package for Social Sciences software (SPSS version 17.0).

RESULTS

There were 454 patients with PHT and bleeding from GV. 301 (66.2%) patients were males and 153 (33.7%) were females. The mean age was 36.58 ± 17 years (4–80 years). 292 (64%) had cirrhosis and 162 (36%) had EHPVO (Table 1). The gastric variceal characteristics of patients with are shown in Table 1.

Gastric Oesophageal varices (GOV1) was present in 16.4% ($n = 48$) of cirrhotics as compared to 7.4% ($n = 12$) of EHPVO. GOV2 was present in 76.7% ($n = 224$) of cirrhotics as compared to 53.1% ($n = 86$) of EHPVO patients. Isolated gastric Varices (IGV1) was seen in 39.5% ($n = 64$) of patients with EHPVO and in 6.8% ($n = 20$) cirrhotics. Of 272 patients with gastroesophageal varices in cirrhosis, 124 (45.5%) had undergone esophageal variceal eradication compared to 51 of 98 (52%) patients with gastroesophageal varices in EHPVO.

Total of 778 injections (436 in cirrhotics; 342 in EHPVO) of NBC were used (Table 2). The mean duration of follow up was 14.7 ± 6.46 months (range 2–22 months). The mean volume of glue injected was 2.89 ± 1.59 ml over a median of 1 session (range: 1–7). The total volume of glue required in cirrhotics was 2.44 ± 1.17 ml and in EHPVO patients was 3.69 ± 1.91 ml and the difference was significant between the two groups ($P = 0.01$). The mean number of sessions required for obturation of GV in cirrhotics was 1.49 ± 0.68 (range 1–4) and in EHPVO was 2.11 ± 0.97 (range 1–7) and this difference was significant ($P = 0.03$). 40.1% ($n = 117$) of cirrhotics required >1 sessions of glue injection as compared to 63% ($n = 102$) of EHPVO patients. More than 2 ml of glue injection for GOV obturation was required in 63% ($n = 102$) of EHPVO as compared to 57.1% ($n = 167$) of cirrhotics. Rebleeding was seen in 10% ($n = 29$) of cirrhotics vs. 13% ($n = 21$) of EHPVO patients and this difference was not significant ($P = 0.87$). Over mean follow up period of 14.7 ± 6.46 months, mortality (15.4% vs. 2.5%, $P = 0.001$) was significant in patients with cirrhosis and EHPVO. Causes of death were hepatorenal syndrome ($n = 22$), septicemia ($n = 13$) and upper gastrointestinal bleeding ($n = 10$) in patients with cirrhosis and upper gastrointestinal bleeding ($n = 2$) and sepsis ($n = 2$) in patients with EHPVO.

Complications of NBC Treatment

No clinically significant embolic complications attributed to NBC were noted during or after the procedure. There was no damage to the endoscopes

DISCUSSION

Soehendra et al.¹⁴ described the association of GV and PHT in 1931. The overall incidence of GV in patients with PHT is 18–70%.^{1,2} GV are the source of 5–10% of all upper digestive bleeding in patients with PHT.¹⁵ The most widely

Table 1 Baseline Characteristics of the Patients.

Characteristics	Cirrhosis	EHPVO	P value
No. of patients	292 (64%)	162 (36%)	
Male:female	201:91	100:62	0.14
Age	46.68 ± 11.13	20.81 ± 9.16	0.001
Etiology			
Alcohol	112 (38.4%)		
HBV	67 (22.8%)		
HCV	36 (12.3%)		
Cryptogenic	77 (26.4%)		
CTP (A/B/C)	58 (19.9%)/154 (52.7%)/80 (27.4%)		
Time interval between bleeding and endoscopic therapy			
<24 h	108 (37%)	84 (51.9%)	0.003
>24 h	94 (32.2%)	53 (32.7%)	0.91
Prevention	90 (30.8%)	25 (15.4%)	0.001
GOV classification			
GOV1	48 (16.4%)	12 (7.4%)	0.006
GOV2	224 (76.7%)	86 (53.1%)	0.001
IGV1	20 (6.8%)	64 (39.5%)	0.001
Form of varix			
F1	0	0	
F2	180 (61.6%)	70 (43.2%)	0.001
F3	112 (38.4%)	92 (56.8%)	0.001

used classification is that proposed by Sarin et al.³ A high portosystemic pressure (>12 mmHg) is not related to the incidence of gastric variceal bleeding as in esophageal varices. This is likely due to the high frequency of spontaneous gastroduodenal shunts.¹⁶ In a study by Sarin et al.,³ fundal varices had a significantly higher bleeding incidence (78% and 55% for IGV1 and GOV2, respectively) than either

GOV1 or IGV2 (10%). In our study of 454 patients, GOV1 was present in 16.4% ($n = 48$) of cirrhotics as compared to 7.4% ($n = 12$) of patients with EHPVO, whereas GOV2 was present in 76.7% ($n = 224$) of cirrhotics as compared to 53.1% ($n = 86$) of patients with EHPVO. IGV1 was seen in 39.4% ($n = 64$) of patients with EHPVO and in 6.8% ($n = 20$) cirrhotics.

Table 2 Outcome of Undiluted NBC Injection in Management of Gastric Varices.

	Cirrhosis ($n = 292$)	EHPVO ($n = 162$)	P value
<2 ml glue 1st session	245 (84%)	112 (69.1%)	0.001
>1 session of glue	117 (40.1%)	102 (63%)	0.001
>2 ml glue for obliteration	167 (57.1%)	102 (63%)	0.27
Total glue (ml)	2.44 ± 1.17	3.69 ± 1.91	0.001
Rebleed	29 (10%)	21 (13%)	0.32
Rebleed <48 h	13 (4.5%)	10 (6.2%)	0.50
Rebleed >48 h	16 (5.5%)	11 (6.8%)	0.67
EVL for esophageal varices	184 (63%)	39 (24%)	0.04
Mean number of sessions	1.49 ± 0.68	2.11 ± 0.97	0.03
Mortality	45 (15.4%)	4 (2.5%)	0.001
Follow up (months)	12.51 ± 4.27	18.6 ± 7.75	–
Overall mean volume of glue injected = 2.89 ± 1.59 ml			
Overall mean follow up in months = 14.7 ± 6.46			
No. of sessions median of 1 (1–7)			

Various endoscopic, interventional radiologic, and surgical therapies have been used for the treatment of gastric variceal bleeding but the success was variable.¹⁷ Transjugular intrahepatic portosystemic shunt (TIPS) is the one of the most commonly recommended procedures for acute gastric variceal bleeding. TIPS and NBC treatment have been shown to be equivalent in the control of acute bleeding, with a similar rate of rebleeding. Compared with NBC, TIPS has been associated with a higher rate of long-term morbidity requiring hospitalization because of an increased incidence of encephalopathy.¹⁸ Cost effective analyses comparing NBC injection with TIPS have suggested that NBC is a safe and cost effective treatment for gastric variceal bleeding.^{19,20} TIPS is available in limited centers.¹⁷ Balloon occluded retrograde transvenous obliteration has been used for GV obliteration, primarily in Japan, as an elective procedure and not suitable for acute gastric variceal bleeding and requires the presence of a spontaneous gastro-renal shunt.²¹

The preferred first line treatment for acute gastric variceal bleeding is endoscopic obliteration with NBC.^{20,22} Endoscopic injection of tissue glue for gastric variceal bleeding was first reported in 1986 by Soehendra et al.¹² Since then, this method has been proved to be effective in the hemostasis of gastric variceal bleeding.^{23–29} NBC, a liquid monomer, undergoes rapid exothermic polymerization on contact with living tissues, and this property of the compound has been used to eradicate and treat GV. The relative efficacy of glue injection in the control of active gastric variceal bleed has been addressed in three randomized trials; it has been compared to sclerotherapy in one trial and variceal ligation in two.^{22,24} Two trials demonstrated better control of bleed with the use of glue injection as compared to sclerotherapy or variceal ligation (89% vs. 62% and 87% vs. 45%)²⁷; the third showed equivalent results as variceal ligation.²² Rebleed was significantly lower with glue injection when compared to variceal ligation (31% vs. 54%)^{22,28} and similar to sclerotherapy. Glue injection achieves variceal eradication in about 75% of patients (range: 50–100%) with rebleed in 23–50% of patients.⁸ It has been suggested that rebleed rates may be reduced with the use of endoscopic ultrasound guided glue injection.²⁴ Billi et al.²⁷ conducted a 24-month follow up of 50 patients who underwent glue injections for GV and reported that acute hemostasis was achieved in 92% of patients. Also Fuster et al.³⁰ reported good results from glue use in pediatric patients. In this study, the success rate of acute hemostasis was 98.4%, comparable with other studies.^{22,29} Indeed, although rare, fatal complications like systemic and pulmonary embolization do occur.^{22,28} Such events are especially commoner in those with large gastro-renal shunts and hepatopulmonary syndrome and caution is required with the use of glue in such patients.⁸ In our study there were no post glue complications. In the present study, the mean volume of glue injected was 2.89

± 1.59 ml over a median of 1 session (range: 1–5), the difference was significant between two groups. Forty percent of cirrhotics required more than one session of glue injection as compared to 63% of EHPVO patients. More than 2 ml of glue injection for GOV obturation was required in 63% of EHPVO as compared to 57.1% of cirrhotics. Rebleeding rates were similar in the two groups. The rebleeding rate of 10–13% observed in this study was higher than that reported by D'Imperio et al.³¹ (3.7%), similar to Dhiman et al.³² (10.3%) but lower to those reported by Huang et al.³³ (23.3%), Tan et al.²² (27%) and Lee et al.²⁴ (44.7%). Simply probing the varix after individual injection is the simplest and most reliable method to confirm variceal obturation.¹⁸ Endoscopic ultrasound is another useful modality to confirm obturation of GV.

We conclude that, in patients with bleeding GV, GOV2 is significantly more common in cirrhotics as compared to patients with EHPVO and IGV1 is significantly more common in patients with EHPVO than in cirrhotics. The preferred endoscopic therapy for gastric variceal bleeding is injection of NBC. Patients with EHPVO require significantly higher total volume of glue and more glue sessions for GV obturation. Rebleeding rates are similar in patients with EHPVO and cirrhosis. There were no post glue complications in either group.

CONFLICTS OF INTEREST

The authors have none to declare.

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