ORIGINAL ARTICLE

Cyanoacrylate Glue versus Band Ligation for Acute Gastric Variceal Hemorrhage - A randomized controlled trial at Services Hospital, Lahore

ISMAIL HASSAN[1], ASMA SIDDIQUE[2], MUHAMMAD IBRAR AZHAR[3]

ABSTRACT

Aim: To compare the efficacy and safety of endoscopic variceal ligation (EVL) with cyanoacrylate injection for the treatment of bleeding gastric varices (GVH).

Methods: Sixty patients with bleeding gastric varices were included in the study. Patients were subjected after randomization to either EVL of gastric varices (group l: 30 patients) or cyanoacrylate injection (group ll: 30 patients). Endoscopic sessions were continued till obliteration of the varices. Clinical as well as biochemical parameters and severity of liver disease were assessed in all patients.The primary endpoint was initial hemostasis which was defined as cessation of bleeding for more than 72 hours.

Results: Control of active variceal bleeding was achieved in 20 patients (80%) in group I and all the patients (100%) in group II. The difference was statistically significant (p =0.03). Re-bleeding was seen in 4 patients (13.3%) in group I and 1 patient in group II (3.3%). Gastric varix obliteration was achieved after one session in 33.3% of patients in group I and 60% of patients in group II, however after 2 sessions it was achieved in 66.7% in group I and 96.7% in group II. After 3 sessions variceal obliteration was achieved in 100% in group l. Fever, chest pain and dysphagia were observed more frequently in group II than in group I. Long term complications including spontaneous bacterial peritonitis, hepatic encephalopathy and hepatorenal syndrome were also observed more frequently group II than in group I.

Conclusion: Cyanoacrylate glue injection is superior to EVL for achieving hemostasis and preventing recurrence of gastric variceal rebleeding but has no advantage over GVL for mortality and complications.

Keywords: Gastroesophageal varices, Cyanoacrylate glue (GVO), Endoscopic variceal ligation (EVL)

INTRODUCTION

Gastroesophageal variceal bleeding is responsible for 10 to 20 percent of all cases of bleeding from upper gastrointestinal tract.[1] In Pakistan, it is the most common cause of upper GI bleed (UGIB). A recent study by Sher et al reported variceal bleed to be responsible for as high as 72.1% of UGIB cases[2]. Although many new treatment techniques have been developed over the past few decades for the management of variceal hemorrhage, it still remains a major cause of death in patients with portal hypertension.

Gastric varices (GV) are less common than esophageal varices (EV), however they may be found in up to 20% of patients with portal hypertension.[3] They are classified according to Sarin classification[4] as shown in figure 1.A recent study by Mir et al[5] found the prevalence of gastric varices in Pakistani patients with portal hypertension to be 11%.

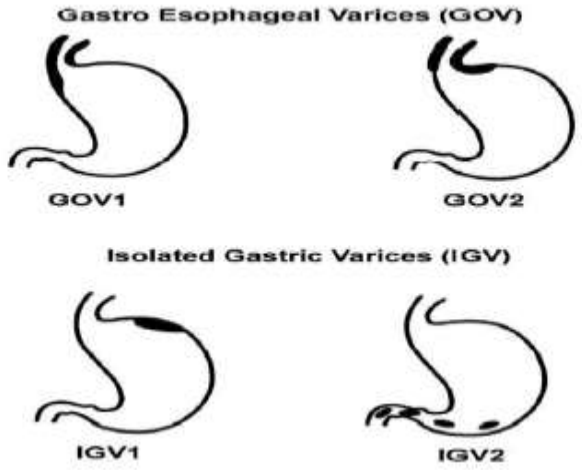
Another local study reported the prevalence to be 15%[6]. Gastric variceal bleeding is associated with a higher mortality and tends to be more severe than esophageal variceal bleeding. It poses a technical challenge for the endoscopist as well.

Cyanoacrylate injection (GVO) and band ligation (EVL) are considered as possible treatment modalities for gastric variceal hemorrhage[7]. In spite of the fact that endoscopic variceal ligation is regarded as the ideal endoscopic treatment for esophageal variceal haemorrhage, the safety and efficacy of this approach for the treatment of GVH is uncertain.Numerous studies have evaluated the role of these two techniques in the management of GVH.A local study by Naseer et al[8] found N-butyl-2-cyanoacrylate sclerotherapy to be highly effective for the treatment of active bleeding gastric varices.Another study from South Asia reported 100% achievement of primary hemostasis following injection of cyanoacrylate[9]. Several Randomized controlled trials have also compared the effectiveness of the two techniques. Tan et al reported that both treatments were equally successful in controlling active bleeding (93.3%)[10]. A recent

[1]MO,BHU Mangini
[2]MO, DHQ Hospital, Okara
[3]MO, BHU, Bansi Khurd
Correspondence to Dr. Ismail Hassan
Email ismail9387@gmail.com

meta-analysis by Ye et al concluded that GVO may be superior to EVL for achieving hemostasis and preventing recurrence of gastric variceal rebleeding but has no advantage over EVL for mortality and complications.[7] Both methods involve complications and technical difficulties, which have to be considered carefully when making a therapeutic decision.So far, there has been no local study comparing the efficacy and safety of the two techniques.There have been studies evaluating the techniques individually[6,8] but there has been no head to head clinical trial which prompted us to conduct this study.Our aim was to assess the therapeutic efficacy and safety of cyanoacrylate injection compared to band ligation in patients with acute GV hemorrhage secondary to liver cirrhosis.

Fig. 1: Sarin classification of Gastric varices[4]



MATERIALS AND METHODS

This randomized control trial was carried out in Gastroenterology unit of services hospital , Lahore during the period of six months starting from janurary 2017 to June 2017. The sample size has been calculated by using OpenEpi calculator with statistical assumptions of 8% alpha error and 95 % confidence interval taking prevalence of gastric varices to be 11%[5] and came out to be 60 patients which was divided equally into two groups, 30 patients in each.All patients with cirrhosis who presented to our hospital with acute gastrointestinal bleeding, or who were already hospitalized and who developed acute gastrointestinal bleeding, received emergency endoscopy unless prevented by severe encephalopathy, severe hemodynamic instability, or the patient's refusal. Only patients who were aged between 20 and 70 years and had endoscopy-proven acute GVH were included.GVH was diagnosed using the following criteria:

1. Clinical signs of bleeding (hematemesis, melena, coffee ground vomiting, or hematochezia).
2. Endoscopic visualization of oozing or spurting, adherent blood clots, white nipple signs, or erosions from or on the GV.
3. Presence of distinct large GV with red-color signs and no other identifiable source of bleeding[12].

Patients with coexistent hepatocellular carcinoma (HCC), varices secondary to non cirrhotic portal hypertension or any terminal illness such as heart failure, uremia, chronic obstructive pulmonary disease, or non hepatic malignancy were excluded from the study.

After admission of all the cases of acute variceal bleeding, they were resuscitated, evaluated with history, physical examination and baseline investigations like complete blood count, renal function test, liver function test, random blood glucose, HBsAg, Anti HCV and ultrasonography of the abdomen were done. The diagnosis of liver cirrhosis was based on the combination of clinical, biochemical, and radiological findings of hepatic failure and portal hypertension, as well as identification of a known cause of cirrhosis.Severity of cirrhosis was assessed according to Child Pugh's classification. All the patients signed an informed consent for procedures of endoscopic therapy. Eligible patients were randomized into two groups using consecutively numbered opaque-sealed envelopes containing the treatment assignment to receive either endoscopic variceal ligation or endoscopic cyanoacrylate injection. All the endoscopists had enough experience in both glue injection and ligation of gastric varices. Treatment sessions were repeated every 2 weeks till the eradication of varices. Subsequent follow-up endoscopy was done every 3 months or for any episode of rebleeding. Follow-up data for rebleeding and mortality were collected until 2 year after enrollment.The primary endpoint was initial hemostasis which was defined as cessation of bleeding for more than 72 hours. If re-bleeding occurred and proved to originate from gastric varices, repeat session of the previous treatment was performed. Secondary endpoints were survival time and complications or death.Variceal obliteration was considered when varices disappeared or reduced to grade 1 and /or when it was not possible to aspirate into the ligation chamber. Re-bleeding was defined as new onset of hematemesis, hematochezia or melena with variceal bleeding within 24 hours of stable vital signs after endoscopic management. Treatment failure was defined as two or more rebleeding episodes from junctional varices or death.

Statistical analysis was performed using SPSS version 21.0 Results were expressed as mean± standard deviation (SD) or number (%). Comparison was made between the mean values using student t

test. Comparison between categorical data [n(%)] was done using Chi square test.

RESULTS

Both groups at the time of inclusion were similar with regard to demographic data, clinical and laboratory findings. There were 40 males (67%) and 20 females (33%). Their age ranged from 25 to 72 years with a mean ± SD of 50.0+4.0 years (Table 1).

All patients underwent endoscopic treatment, either band ligation or endoscopic cyanoacrylate injection. Initial hemostasis was achieved in 24 patients in group I (80%) and all 30 patients in group II (100%).The difference was statistically significant (p value =0.03).

Re-bleeding was seen in total 5 patients: 4 patients (13.3%) in the EVL group and only 1 patients (3.3%) in the cyanoacrylate group.However, the difference was statistically insignificant (p value=0.16). Treatment failure was encountered in only 1 patient belonging to the cyanoacrylate group.The number of sessions needed for obliteration of varices ranged from 1-3 (mean 2.1±0.7) in group I and from 1-2 (mean 1.6±0.6) in group II with no statistical significance. Variceal obliteration was achieved by one session in 10 patients in group I and in 18 patients in group II (p=0.04), while it was achieved after the second session in 20 patients in group I versus 29 patients in group II (p=0.002). The remaining 10 patients in group I achieved eradication after 3 sessions (Table 2).

Overall patients in Group II developed more complications than Group I. The most common complication was chest pain (3 patients in Group II i.e., 10%). Likewise, Long term complications as hepatic encephalopathy and hepatorenal syndrome (HRS) were also observed more frequently in patients of group II than group I, but with no statistical significance. Fatal bleeding from huge post sclerotherapy ulcer was seen in 1 patient in group II and in none in group I.Death occurred in one case (3.3%) in group I due to HRS and in 2 cases (6.7%) in group II, 1 died from massive bleeding and 1 due to HRS (Table 3).

Table 1: Demographic characteristics of patients treated with EVL or cyanoacrylate at randomization

	EVL	**Cyanoacrylate**
No. of patients	30	30
Age (years)(mean ±SD)	49 ± 5	51 ± 3
Sex: male/female	19/11	21/9
Etiology of PH		
Hepatitis C	20	22
Hepatitis B	6	4
Other	4	4
Severity of liver disease		
Child A	6	8
Child B	17	15
Child C	7	7
Laboratory investigations		
Serum albumin (gm %)	3.28 ± 0.4	3.12 ± 0.6
Serum bilirubin (mg %)	2.1 ± 0.7	2.5 ± 0.9
Prothrombin concentration	63.2 ± 8.2	59.7 ± 10.6
Hemoglobin (gm %)	8.7 ± 1.3	8.3 ± 1.6
Platelet count / mm^3	230 ± 61.2	215 ± 75.3
Serum creatinine (mg %)	0.94 ± 0.52	1.0 ± 0.42
Hemodynamic instability	4	8

Table 2: The results of endoscopic therapy in both EVL and cyanoacrylate groups

Endoscopic therapy	**Group I (EVL)**	**Group II (Cyanoacrylate)**	**p value**
Initial hemostasis	24/30 (80%)	30/30 (100%)	0.03
No. of sessions; mean ± SD	2.1 ± 0.65-7	1.6 ± 0.57-9	NS
Re-bleeding	4/30 (13.3%)	1/30 (3.3%)	0.16
Treatment failure	0/30	1/30 (3.3%)	NS
Variceal obliteration			
After one session	10 (33.3%)	18 (60%)	0.04
After two sessions	20 (66.7%)	29 (96.7%)	0.002
After three sessions	30 (100%)		

EVL: endoscopic variceal ligation. Chi square test used for comparison.

Table 3: Complications associated with EVL or cyanoacrylate injection, showing no statistical difference between both groups

Complications	**Group I (EVL)**	**Group II (Cyanoacrylate)**	**P value**
Fever	0/30	1/30 (3.3%)	NS
Chest pain	1/30 (3.3%)	3/30 (10%)	0.30
Dysphagia	0/30	2/30 (6.7%)	NS
Fatal bleeding from variceal ulcer	0/30	1/30 (3.3%)	NS
Spontaneous bacterial peritonitis	0/30	0/30	NS
Hepatic encephalopathy	1/30 (3.3%)	2/30 (6.7%)	0.55
Hepatorenal syndrome	0/30	1/30 (3.3%)	NS
Death	1/30 (3.3%)	2/30 (6.7%)	0.55

EVL: endoscopic variceal ligation. Fisher's test and Chi square test used

DISCUSSION

Gastric varices (GV) account for 10-30% of all variceal hemorrhage. GVH is associated with higher mortality compared to EVH.GVH also poses a diagnostic challenge because the gastric mucosal folds, blood pooling in the fundus, and high posterior wall (the usual site of GVH) are confusing[10] Based on Sarin's classification, gastric varices can be classified as GOV1, GOV2, IGV1 and IGV2. Our study included patients with any of the above types of gastric varices. Recent practice guidelines recommend EVO for treating bleeding from GOV2 or IGV1[13].

Our study showed that GVO proved to be superior to band ligation for acute GV bleeding with higher initial hemostasis rates (100% vs 80%) with p value of 0.03. This was in contrast with the findings of many other studies who found the difference in initial hemostasis rates to be statistically insignificant[13-16]. However it was consistent with the conclusion of meta-analysis conducted by Ye et al[7]. Statistical non-significance could be attributed to relatively small number of patients with active bleeding in each study.In fact a pooled analysis by Park et al[15] showed hemostasis rate to be significantly higher in the GVO group thus hinting at need for a large scale multicenter clinical trial. In our study, re-bleeding occurred in 4 pts in EVL group (13.3%) vs 1 patient in cyanoacrylate group (3.3%). This was consistent with the findings of previous studies reporting the difference in re-bleeding rates to statistically insignificant[10,13,14,16]. However Park et al[15] found out the difference in rebleeding rates to be statistically significant with a p value of 0.004 (15.1% vs 3.6%). The higher rebleeding and recurrence rate in EVL patients may be attributable to the limitation of EVL's effect on only the superficial collaterals in the mucosal and submucosal layers. In contrast, GVO may obliterate collaterals over a wider area and in deeper layers[10]. The relatively lower re-bleeding rates in our study were probably due to exclusion of cases with advanced hepatocellular carcinoma which is a major risk factor of rebleeding[17]. A patient suffered from massive rebleed after cyanoacrylate injection and died. This patient was having Child class C liver cirrhosis. As expected, a higher Child class classification was associated with a greater number of complications. No difference in mortality rate was observed between the two groups (p value=0.55).This was in line with the findings of El amin et al[14]. However, Park et al[15] and Lo et al[16] reported the difference in mortality rates to be statistically significant.

CONCLUSION

GVO is superior to EVL for achieving hemostasis and preventing recurrence of gastric variceal rebleeding but has no advantage over EVL for mortality and complications.

REFERENCES

1. Sher F, Ullah RS, Khan J, Mansoor SN, Ahmed N. Frequency of different causes of upper gastrointestinal bleeding using endoscopic procedure at a tertiary care hospital. Pakistan Armed Forces Medical Journal. 2014 Sep 30;64(3):410-3.
2. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. N Engl J Med 2008; 359:928-37.
3. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992; 16: 1343-9.
4. Sarin SK, Kumar A. Endoscopic treatment of gastric varices. Clinics in liver disease. 2014 Nov 1;18(4):809-27.
5. Mir AW, Khan AA, Chaudry AA, Mir S, Shahzadi M, Ahmed N. Frequency of gastric varices in patients with portal hypertension based on endoscopic findings. Pakistan Armed Forces Medical Journal. 2017 Feb 1;67(1):67-71.
6. Mumtaz K, Majid S, Shah H, Hameed K, Ahmed A et al. Prevalence of gastric varices and results of sclerotherapy with N-butyl 2 cyanoacrylate for controlling acute gastric variceal bleeding. World J Gastroenterol 2007; 13:1247-51
7. Ye X, Huai J, Chen Y. Cyanoacrylate injection compared with band ligation for acute gastric variceal hemorrhage: a meta-analysis of randomized controlled trials and observational studies. Gastroenterology research and practice. 2014.
8. Naseer M, Khan AU, Gillani FM, Saeed F, Ahmed S. Determination of frequency and treatment outcome in patients of fundal varices presenting with upper gastrointestinal bleeding. Pak A F Ml J. 2012;62(4):483-6.
9. Jha A, Sharma S, Khadga PK, Pathak R, Poudyal S, Hamal R. Glue therapy for bleeding gastric varices: a single tertiary center experience in Nepal. J Inst Medicine. 2017 Oct 31.
10. Tan PC, Hou MC, Lin HC, Liu TT, Lee FY. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N- butyl- 2- cyanoacrylate injection versus band ligation. Hepatology. 2006 Apr 1;43(4):690-7.
11. Tantau M, Crisan D, Popa D, Vesa S, Tantau A. Band ligation vs. N-Butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: a prospective follow-up study. Annals of Hepatology: Official Journal of the Mexican Association of Hepatology. 2014 Jan 1;13(1).
12. de Franchis R; Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-768.
13. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology 2001;33:1060-1064.
14. El Amin H, Abdel Baky L, Sayed Z, Abdel Mohsen E, Eid K, Fouad Y, et al. A randomized trial of endoscopic variceal ligation versus cyanoacrylate injection for treatment of bleeding junctional varices. Trop Gastroenterol 2010;31:279
15. Park SJ, Kim YK, Seo YS, Park SW, Lee HA, Kim TH,. Cyanoacrylate injection versus band ligation for bleeding from cardiac varices along the lesser curvature of the stomach. Clinical and molecular hepatology. 2016 Dec;22(4):487.
16. Lo GH, Lin CW, Perng DS, Chang CY, Lee CT, Hsu CY, Wang HM, Lin HC. A retrospective comparative study of histoacryl injection and banding ligation in the treatment of acute type 1 gastric variceal hemorrhage. Scandinavian journal of gastroenterology. 2013 Oct 1;48(10):1198-204.
17. Chen WC, Hou MC, Lin HC, et al. Feasibility and potential benefit of maintenance endoscopic variceal ligation in patients with unresectable hepatocellular carcinoma and acute esophageal variceal: a controlled trial. Gastrointest Endosc. 2001;54:18–23