PREDICTORS OF MORTALITY WITHIN 8 WEEKS AFTER ENDOSCOPIC TREATMENT OF GASTRIC VARICEAL BLEED WITH N-BUTYL 2-CYANOACRYLATE IN CIRRHOTIC PATIENTS

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ABSTRACT

Objective: To assess the predictors associated with mortality within 8 weeks in patients undergoing endoscopic N-butyl-2-cyanoacrylate treatment.

Study Design: Prospective comparative study.

Place and Duration of Study: Department of Gastroenterology, Services Institute of Medical Sciences, Lahore Pakistan, from Mar 2018 to Mar 2019.

Methodology: A total of 106 patients of gastric variceal bleed were enrolled in the study. Tissue glue was injected into the varix endoscopically and mortality within 8 weeks after endoscopic intervention was noted.

Results: Among the enrolled patients, 65 (61.3%) were male and 41(38.7%) were female. Mortality was noted in 19 (17.9%) patients within 8 weeks after endoscopic therapy. Chi-square analysis showed creatinine >1.5, Child Pugh score >9, MELD score >18, re-bleeding within 7 days, low blood pressure <90/60 at presentation and hepatic encephalopathy as significant predictors of mortality (p<0.005).

Conclusion: Cirrhotic patients undergoing endoscopic injection of gastric varix with N-butyl 2-cyanoacrylate after gastric variceal bleed have high risk of death within 8 weeks.

Keywords: Cirrhosis, Gastric varices, Mortality, N-butyl 2-cyanoacrylate, Outcome, Predictors.

INTRODUCTION

Gastric varices are the abnormal dilated submucosal veins in the stomach formed as a result of portal hypertension or splenic vein thrombosis. The best test to diagnose and classify the gastric varices is upper GI endoscopy. Classification of gastric varices is based on its location in the stomach (Sarin's classification) or according to their form, location, and color (Hashizome classification)[1]. Gastric variceal bleed is a serious complication of liver cirrhosis, associated with significant morbidity and mortality[2,3]. N-butyl 2-cyanoacrylate has shown promising results but mortality among these patients is still high. According to an estimation the frequency of gastroesophageal and gastric varices in patients of cirrhosis is 50% and 25% respectively[4-5]. Though gastric varices bleed less frequently when compare to esophageal varices but the episodes of bleed are far more severe and are associated with significant mortality ranging from 15-30%[6-7]. Also the rate of re-bleeding after spontaneous remission is high in gastric varices[8,9]. Endoscopic band ligation is the procedure of choice for esophageal varices both in primary and secondary prophylaxis but is less effective in case of gastric variceal bleed primarily due to low rate of initial bleeding control (26-51%) and high rate of rebleeding (60-90%)[10]. Also increased incidence of encephalopathy has been observed with TIPS. Though endoscopic glue injection has shown high success rates but mortality among survivors is still high. The factors leading to death in patients with gastric variceal bleed after endoscopic intervention are not addressed widely.

We planned to study the predictors associated with mortality within 8 weeks after N-butyl-2-cyanoacrylate therapy of gastric varices.

METHODOLOGY

This prospective comparative study was conducted at Gastroenterology department, SIMS/ Services Hospital Lahore, from March 2018 to March 2019. Study was conducted after Institutional Review Board approval (Ref No. IRB/2018/ 375/SIMS). Sample size of 106 was calculated using 90% confidence interval, 5% margin of error and taking expected outcome of 11%. Male and female patients aged 18-60 years having gastric variceal bleed with underlying liver cirrhosis were included in the study. Non probability consecutive sampling technique was used. Demographic data, history, clinical & laboratory parameters of enrolled patients was recorded on a proforma. Standard treatment viz vasoconstrictors (terlipressin/octreotide), proton pump inhibitor, and antibiotics were given to all the patients. Blood transfusion, where required was given to keep the hemoglobin around 8.5 g/dL. Upper GI Endoscopy and Cyanoacrylate glue treatment was

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Received: 11 Sep 2019; revised received: 06 Aug 2020; accepted: 31 Aug 2020

performed by experienced gastroenterologist within 24 hours of admission as recommended by Seewald *et al*, and other authors[11-14]. Patients having source of bleeding other than gastric varices (esophageal varices gastric ulcer, gastric antral vascular ectasia) were excluded. Patients having rebleeding within 12 hours of intervention were also excluded from the study.

Upper GI Gastroscopy was performed in all the patients to classify the gastric varices according to Sarin classification. Disposable sclerotherapy injection needle of 21G was used in all procedures. Lipiodol was filled in the catheter to fill the dead space. Equal quantity of Lipiodol and tissue glue was filled in a 5cc syringe. Maximum amount used was 2ml. The gastric varix was positioned appropriately with scope in retroflex position and gastric varix was punctured with needle followed by rapid push of N-butyl-2 cyanoacrylate and Lipiodol mixture. This was followed by a rapid push of Lipiodol by an expert endoscopy technician (quantity pre-calculated according to the dead space). All the patients were monitored for 24 hours for recurrence of bleeding. Follow up endoscopy was performed every 4 weeks to assess the varix obliteration and any further need of sessions.

SPSS-22 was used for Statistical analysis. Mean ± SD was calculated for quantitative variables, frequency and percentage were calculated for qualitative variables. Chi-square test was used to assess the difference between the survivors and non-survivors. The *p*-value of <0.05 was taken as statistically significant.

RESULTS

A total of 106 patients (61.3% male and 38.7% female) were included. Mean age ± SD was 51.47 years ± 7.31. Mean Hemoglobin ± SD was 10.7 g/dl ± 1.85. Mean creatinine ± SD was 1.2 mg/dl ± 0.51. Mean bilirubin ± SD was 2.02 mg/dl ± 0.74. Mean Child score was 7.4 and mean MELD score at hospital admission was 14.6. The cause of liver cirrhosis was HCV infection in 90 (84.9%) patients, HBV infection in 10 (9.4%) patients and idiopathic in 6 (5.7%) patients. All the patients were given N-butyl 2-Cyanoacrylate glue therapy. No significant adverse event of the intervention was observed. The overall mortality within 8weeks after endoscopic treatment was noted in 19 patients (17.9%) (figure). Chi-aquare analysis of factors showed increased creatinine >1.5 (p<0.001), child pugh score >9 (p<0.001), MELD score >18 (p<0.001), rebleeding within 7 days (p=0.006), low BP <90/60 at admission (p=0.025) and hepatic encephalopathy (p=0.035) as significant predictors of mortality (table).

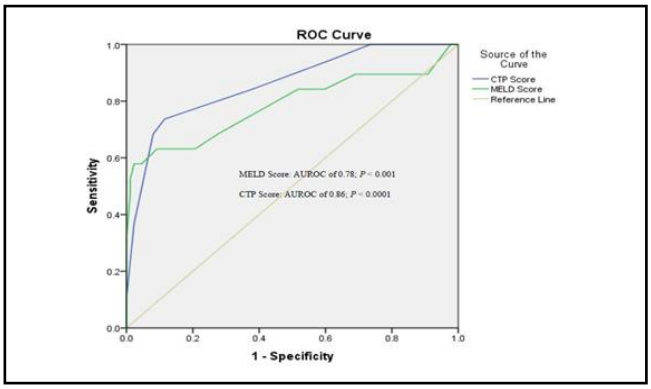

Figure: ROC (Receiver operating characteristic) curve of MELD and CTP Scores in predicting 8-week mortality after gastric variceal bleed.

Table-I: Variables associated with 8-week mortality.

Variable		Mortality n=19 (17.9%)	Survival n=87 (82.1%)	*p*-value
Age (Year)	>60	4 (3.8%)	12 (11.3%)	0.423
	<60	15 (14.2%)	75 (70.8%)	
Gender	Male	12 (11.3%)	53 (50%)	0.856
	Female	7 (6.6%)	34 (32.1%)	
Etiology of Cirrhosis	Hepatitis C	15 (14.2%)	75 (70.8%)	0.579
	Hepatitis B	3 (2.8%)	7 (6.6%)	
	Idiopathic	1 (0.94%)	5 (4.7%)	
Creatinine	>1.5	13 (12.3%)	12 (11.3%)	<0.001
	<1.5	6 (5.7%)	75 (70.8%)	
Child-Pugh Score	>9	13 (12.3%)	15 (14.1%)	<0.001
	<9	6 (5.7%)	72 (66.9%)	
MELD Score	>18	15 (14.2%)	21 (19.8%)	<0.001
	<18	4 (3.7%)	66 (62.3%)	
Ascites	Yes	7 (6.6%)	42 (39.6%)	0.055
	No	12 (11.3%)	45 (42.5%)	
Encephalopathy	Yes	10 (9.4%)	27 (25.5%)	0.035
	No	9 (8.5%)	60 (56.6%)	
Blood in Stomach	Yes	6 (5.7%)	39 (36.8%)	0.290
	No	13 (12.3%)	48 (45.2%)	
Active Bleeding on EGD	Yes	8 (7.5%)	31 (29.3%)	0.596
	No	11(10.4%)	56 (52.8%)	
Rebleeding in 7 days	Yes	7 (6.6%)	10 (9.4%)	0.006
	No	12 (11.3%)	77 (72.6%)	
Low BP at Admission	Yes	10 (9.4%)	23 (21.7%)	0.025
	No	09 (8.4%)	64 (60.4%)	
Concomitant HCC	Yes	1 (0.94%)	10 (9.4%)	0.420
	No	18 (17%)	77 (72.6%)	
Hb at Admission	>8g/dl	14 (13.2%)	77 (72.6%)	0.093
	<8g/dl	5 (4.7%)	10 (9.4%)	
Blood Transfusion	Yes	3 (2.8%)	26 (24.5%)	0.212
	No	16 (15.1%)	61 (57.5%)	

DISCUSSION

Current available treatment options for gastric varices are beta blockers, somatostatin (octreotide) & vasopressin (terlipressin) analogues, tissue glue (N-butyl-2-cyanoacrylate), balloon occluded retrograde

transvenous obliteration (BRTO), transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation[12]. Both, balloon occluded retrograde transvenous obliteration (BRTO) and transjugular intrahepatic portosystemic shunt (TIPS) are considered as valuable first line treatment options for gastric variceal bleed management but high cost of these procedures and lack of expertise make endoscopic glue injection a cost effective strategy in resource-constrained countries[13].

Gastric variceal bleed is associated with significant risk of mortality, even after successful endoscopic hemostasis. In our study we evaluated the mortality and its predictors in patients with bleeding gastric varices within 8-week after N-butyl 2-Cyanoacrylate injection. The overall mortality in our study was observed in 19 (17.7%) patients. Fifteen variables were analyzed in our study, out of which three variables were found to be independent predictors of mortality within 8 weeks: impaired renal function, high Child-Pugh score >9 and high MELD score >18. Three variables: hepatic encephalopathy, rebleeding within 7 days & low blood pressure at admission were significant on univariate analysis but lost their predictive significance on multivariate logistic regression analysis. A study similar to ours was performed by Teng *et al*, at Chang Gung Memorial Hospital Taiwan in 2014[15]. They studied the mortality within 6 weeks and its predictors after N-butyl cyanoacrylate injection. They included 132 patients and the mortality was 16.7% within 6 weeks. Impaired creatinine, child score >9, MELD score >18, rebleeding within 5 days, and Acute on chronic liver failure were independent predictors of mortality. The rate of rebleeding in our study was 19% within first 7 days. Similar rebleeding rates were reported by Prachayakul *et al*, and Jairath *et al*[7,16]. This risk of rebleeding after gastric variceal injection is related to increased portal pressure after endoscopic intervention[17]. Another study by Avgerinos *et al*, showed that endoscopic sclerotherapy cause a sustained increase in hepatic venous pressure gradient compared to band ligation, leading to increased risk of rebleeding in this group[18]. A similar study was conducted by Chang *et al*, in 2010 in Seoul, Korea. They evaluated the factors affecting the outcome after N-butyl 2-cyanoacrylate injection in patients with gastric variceal bleed[19]. Pack cell transfusion and high MELD scores were identified as important predictive factors of re-bleeding and mortality. A study conducted at Taichung Veterans General Hospital Taiwan in August 2000 on 118 patients with gastric variceal bleed showed that concomitant hepatocellular carcinoma was associated with early re-bleeding[20]. Bambha *et al*, conducted a study at Mayo Clinic, Minnesota on 256 patients with liver cirrhosis and found that MELD score >18, pack cell transfusion >4 in first 24 hours and ongoing bleeding at endoscopy were significant predictors of 6 weeks mortality[21]. Another study by Han *et al*, showed that the deranged liver enzymes, impaired serum creatinine, active bleeding on index endoscopy and primary treatment failure were the predictors of mortality after gastric variceal hemorrhage[22]. Chen *et al*, also conducted a similar study at in Taiwan on 128 cirrhotic patients who presented with variceal bleed and found that high MELD score, hypotension and use of b-blocker after an episode of rebleeding were associated with 6-week mortality[23].

CONCLUSION

Mortality rate within 8 weeks after N-butyl-2-cyanoacrylate injection is high (17.9%) and renal impairment, high MELD and high CTP score were independent mortality predictors. Mortality risk can be stratified by identifying these predictors.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Wani ZA, Bhat RA, Bhadoria AS, Maiwall R, Choudhury A. Gastric varices: classification, endoscopic and ultrasonographic management. J Res Med Sci 2015; 20(12): 1200-7.
2. Boregowda U, Umapathy C, Halim N, Desai M, Nanjappa A, Arekapudi S. Update on the management of gastrointestinal varices. World J Gastroin Pharmacol Therapeut 2019; 10(1): 1-5.
3. Hejda V. Late complications of liver cirrhosis-management of gastrointestinal bleeding in the presence of portal hypertension. Vnitr Lek 2016; 62(Suppl-2): 10-17.
4. Haq I, Tripathi D. Recent advances in the management of variceal bleeding. Gastroenterol Report 2017; 5(2): 113-26.
5. Than NN, Zhu Q, Qi X, Tian Y, Vitin A, Tomescu D, et al. Liver cirrhosis: update and current challenges. Zagreb, Croatia: Intech Open: 2017. [Internet] Available at https://www.intechopen.com/books/5960.
6. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015; 64(11): 1680-4.
7. Jairath V, Rehal S, Logan R. Acute variceal haemorrhage in the United Kingdom: Patient characteristics, management and outcomes in a nationwide audit. Dig Liver Dis 2014; 46(5): 419–6.
8. Girotra M, Raghavapuram S, Abraham RR, Pahwa M, Pahwa AR, Rego RF. Management of gastric variceal bleeding: role of endoscopy and endoscopic ultrasound. World J Hepatol 2014; 6(3): 130-34.
9. Crisan D, Tantau M, Tantau A. Endoscopic management of bleeding gastric varices - an updated overview. Curr Gastroenterol Rep 2014; 16(10): 413-16.
10. Garcia-Pagan JC, Barrufet M, Cardenas A. Manage-ment of gastric varices. Clin Gastroenterol Hepatol 2014; 12(6): 919-8.
11. Hassan I, Siddique A, Azhar MI. Cyanoacrylate glue versus band ligation for acute gastric variceal hemorrhage - a randomized

controlled trial at services hospital, Lahore. Pak J Med Health Sci 2018; 12(1): 173-6.
12. Goral V, Yılmaz N. Current approaches to the treatment of gastric varices: Glue, Coil Application, TIPS, and BRTO. Med 2019; 55(7): 335-38.
13. Parvinian A, Gaba RC. Outcomes of TIPS for treatment of gastroesophageal variceal hemorrhage. Semin Inter Radiol 2014; 31(03): 252-7.
14. Seewald S, Ang TL, Imazu H, Naga M, Omar S, Groth, S, et al. A standardized injection technique and regimen ensures success and safety of N-butyl-2- cyanoacrylate injection for the treatment of gastric fundal varices (with videos). Gastrointest Endosc 2008; 68(3): 447–4.
15. Teng W, Chen WT, Ho YP, Jeng WJ, Huang CH, Chen YC, et al. Predictors of mortality within 6 weeks after treatment of gastric variceal bleeding in cirrhotic patients. Med 2014; 93(29): e321-24.
16. Prachayakul V, Aswakul P, Chantarojanasiri T. Factors influencing clinical outcomes of Histoacryl glue injection-treated gastric variceal hemorrhage. World J Gastroenterol 2013; 19(15): 2379–7.
17. Abraldes JG, Villanueva C, Banares R, Aracil C, Catalina MV, Carlos J, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008; 48(2): 229–6.
18. Avgerinos A, Armonis A, Stefanidis G, Mathou N, Vlachogiannakos J, Kougioumtzian A, et al. Sustained rise of portal pressure after sclerotherapy, but not band ligation, in acute variceal bleeding in cirrhosis. Hepatol 2004; 39(6): 1623–30.
19. Chang YJ, Park JJ, Joo MK, Lee BJ, Yun JW, Yoon DW, et al. Long-term outcomes of prophylactic endoscopic histoacryl injection for gastric varices with a high risk of bleeding. Dig Dis Sci 2010; 55(8): 2391-97.
20. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. Gastrointest Endosc 2000; 52(2): 160-7.
21. Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK. Predictors of early rebleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut 2008; 57(6): 814–20.
22. Han ML, Chen CC, Kuo SH, Hsu WF, Liou JM, Wu MS, et al. Predictors of in-hospital mortality after acute variceal bleeding in patients with hepatocellular carcinoma and concurrent main portal vein thrombosis. J Gastroenterol Hepatol 2014; 29(2): 344-51.
23. Chen WT, Lin CY, Sheen IS, Huang CW, Lin TN, Lin CJ, et al. MELD score can predict early mortality in patients with rebleeding after band ligation for variceal bleeding. World J Gastroenterol 2011; 17(16): 2120–25.