EFFICACY OF THROMBIN FIBRIN GLUE AND SCLEROSANT IN THE MANAGEMENT OF BLEEDING GASTRIC VARICES
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ABSTRACT: Gastric varices are noted in up to 20 % of patients with portal hypertension, and are more common in those with non-cirrhotic etiology¹. They bleed at lower portal pressures, bleed more severely and are associated with higher rates of rebleed, encephalopathy and mortality¹,²,³. Variceal obliteration using tissue adhesives such as N-butyl cyanoacrylate leading to plugging and thrombosis of the gastric varices is currently the first line management option for obliteration of the gastric varices³. Although various options have been proposed, gold standard for management of gastric variceal bleeds is yet to be defined. We theorized that injection of the gastric varices using thrombin based glue followed by injection of a sclerosant shall be effective in optimum sclerotherapy and eradication of gastric varices. MATERIAL AND METHODS: All patients presenting with gastric variceal bleed were offered sclerotherapy with Thrombin fibrin based glue and sclerosant (TFG/S). During the study period 18 patients were enrolled in the TGF/S group. 21 patients underwent variceal plugging with n-butyl cyanoacrylate (NBC). There was no significant difference in age/sex, duration of bleed or time interval between onset of bleed and endotherapy. RESULTS: Patients undergoing endotherapy with TGF/S had less episodes of bleed, and greater eradication of varices. CONCLUSION: The results with thrombin/fibrin glue and sclerotherapy are highly encouraging. Well-designed trials need to be performed to evaluate its efficacy. KEYWORDS: Gastric varices; Thrombin Sclerotherapy.

INTRODUCTION: Gastric varices are noted in up to 20 % of patients with portal hypertension, and are more common in those with non-cirrhotic etiology.¹ Although portal hypertension is the common underlying etiology of both esophageal and gastric varices, they behave differently. Gastric varices often bleed at lower portal pressures than esophageal varices, bleeds more severely than esophageal varices, and are associated with higher rates of rebleed, encephalopathy and mortality.¹,² It is therefore not surprising that the therapeutic strategies like pharmacotherapy, sclerotherapy and balloon tamponade that have demonstrated good efficacy in the management of esophageal varices, have not shown similar results in the management of gastric varices.

While endoscopic variceal ligation (EVL) has more or less been accepted as a standard of care for the management of acute variceal bleed and primary prophylaxis of esophageal varices, definitive therapy for gastric varices is still under evolution. Although various therapeutic options like pharmacologic, endoscopic, radiological and surgical have been proposed for management of gastric varices, gold standard for treatment is yet to be defined.
Sclerotherapy of the gastric varices using ethanolamine oleate, tetradecyl sulphate or absolute alcohol, has been possibly the oldest endotherapy modality tried. In the setting of acute bleed, success rates from 67% to 100% have been reported by some investigators. However as compared to bleeding esophageal varices, sclerotherapy of gastric varices is less effective, requires larger amounts of sclerosants, and associated with higher incidence of procedural complications. Rebleeds have been reported in up to 34% - 89% of patients. Greater blood flow through the gastric varices, leading to rapid washout of the sclerosant has been proposed to be the most likely cause.

Variceal obliteration using tissue adhesives such as N butyl cyanoacrylate leading to plugging and thrombosis of the gastric varices is currently the first line management option for both acute bleeds and secondary prophylactic obliteration of the gastric varices. When compared with sclerotherapy, tissue adhesives have been shown to achieve better homeostasis and lower rates of rebleed. A number of complications (mainly thrombotic) have been reported in association of tissue adhesives and concerns about potential carcinogenesis have been raised. In addition great care and experience is required to prevent needle impaction into the tissue adhesive and potential damage to the endoscope.

There had been some interest in the use of human thrombin +/- fibrin for achieving thrombosis of the gastric varices. Thrombin principally affects homeostasis by catalyzing the conversion of fibrinogen to fibrin monomers, which spontaneously aggregates to form a week fibrin clot. Thrombin also converts factor XIII to XIIIa, which converts these monomers to a cross linked fibrin polymer. It also has other effects on homeostasis such as platelet aggregation. 1000 IU of thrombin is estimated to clot approximately one liter of blood in < 60 seconds. Initial studies utilizing bovine thrombin reported a success rate of approximately 96% to 100 % in achieving homeostasis of bleeding gastric varices. Subsequent short series with human thrombin reported similar results.

Reviewing the literature utilizing thrombin based glue and sclerotherapy of the bleeding gastric varices, it is apparent that sclerotherapy has promising results in the initial control of bleeding gastric varices. However, the rebleed rate is high. Although the exact cause of this high rate of post sclerotherapy recurrence of bleeding is not known, it possibly is due to rapid washout of the sclerosant from the gastric varices.

We therefore theorized that injection of the sclerosant after achieving thrombosis of the gastric varices by initial injection of thrombin- fibrin glue may be effective in achieving adequate sclerotherapy of the gastric varices.

**AIM OF THE PRESENT STUDY:**
1. To evaluate the effect of sclerotherapy of gastric varices with conventional sclerosant after injection of varices with thrombin based glue (TFG/S).
2. To compare the efficacy of thrombin fibrin glue with N- butyl cyanoacrylate (NBC) glue for bleeding gastric varices.

**MATERIAL AND METHODS:** As per our protocol of management of active upper GI bleeds, endoscopy is performed as soon as possible after admission, once the patients are
hemodynamically stable and hemoglobin level is approx. 6 to 7 gm/dl. All patients, who have deranged coagulation profile received 15 ml/kg of fresh frozen plasma prior to/ or during gastroscopy. All patients with a diagnosis of portal hypertension, received injection terlipressin 1mg in the emergency room, soon after presentation and then 1 mg every six hourly. In other patients, where the bleed from gastric or esophageal varices was diagnosed during gastroscopy, terlipressin was started during or immediately after the procedure and continued for at least 24 hrs after endotherapy. SB tube was inserted wherever indicated prior to definitive procedure.

Thrombin fibrin glue (TFG) is available in India as 0.5ml and 1 ml kits, containing two components; fibrinogen 70 mg/ml and thrombin 500IU/ml. An applicator with two mixing chambers and one plunger guide is also supplied with the kit. After reconstitution, the concentration of reconstituted thrombin was kept at 250 IU/ml. Fibrinogen solution was also appropriately diluted. A standard forward viewing gastroscope and a 20G disposable sclerotherapy needle was used for glue injection. The glue was initially injected, followed by 0.5 ml injection of distilled water (to flush the sclerotherapy needle), followed 15 to 30 seconds later by 2 ml of sclerosant injection polidocanol.

The patients, who had earlier received treatment with NBC and had presented with rebleed, were treated with NBC only while others who had presented with gastric variceal bleed for the first time were offered therapy with either NBC or TFG/S after taking consent. A relook gastroscopy was done in all patients within 24 to 48 hours after the first session of glue injection. Thereafter these patients were followed up after every 2-3 weeks and repeat therapy was done till the varices disappeared, or there was no bleed from the varix even after puncturing the residual varix with sclerotherapy needle at multiple sites. Patients were subsequently followed up for at least 6 months after the last session of endotherapy.

RESULTS: During the study period, a total of 39 patients (33 males and 6 females) with gastric variceal bleed were enrolled. 35 patients had presented with bleed for the first time while 4 patients presented with rebleed and had earlier received treatment with NBC. 18/35 patients gave consent for therapy with TFG/S. Rest 17 were treated with NBC. There were thus total 18 patients in the TFG/S and 21 (17 new and 4 rebleed) patients in the with NBC group.

The mean age of patients in TFG/S was 45.9 years and in the NBC group was 46.1 years. There was no significant difference in age/sex or etiology of portal hypertension in either group. The mean hemoglobin at the time of admission in the TGF/S group was 8.35 gms/dl (range: 2.2 - 12.1), while in the NBC group 7.9 gms/dl (range: 2.8 -10.8). There was no difference in the average number of sessions required per patient. The time between onset of bleed and gastroscopy ranged from 4 hrs to 5 days. In NBC group, 38 % reported within first 12 hrs; > 75% at/within 24 hrs; > 90% within 48 hrs, while in the TGF/S group, 33% within 12 hrs; > 66% at/within 24 hrs; > 75% within 48 hrs).

Rebleed: During the study period, rebleed was recorded in 4/21 patients (23.8%) in the NBC group and in 2/18 (11%) in the TFG/S group. On endoscopy, in NBC group, the varices were noted to be ulcerated, with extruding cast recorded in two cases, clean based ulcer in one and ulceration with SRH in one cases. In TFG/S group, clean based ulcer at the site of injection was recorded in one case and active bleed in one case.
Final Outcome: By the end of the study, follow up was available in 15/18 in the TGF/S group and ranged from 2 weeks to 15 months. 3 patients expired; one each due to ATT induced hepatitis, HCC and unrelated cardiac illness. Both patients with rebleed were managed with reinjection with favorable outcome. At endoscopy on follow up varices were noted to have disappeared in 9/18 patients, while varices were decreased in size in 4/18 patients. Two patients had persistent large varix one out of which was thrombosed. Thus 13/15 (86.6 %) of patients in TGF/S group met the study objective of disappearance or markedly decrease in the size of the varices by the end of study period.

Among the NBC group, follow up was available on 16/21 patients and ranged from 3 months to 18 months. One patient expired during hospitalization due to bleed related hepatic dysfunction and uncontrolled hemorrhage. At endoscopy on last follow up varices were noted to have disappeared in 4/16 patients, decreased in size in 5/16 patients. 6 patients had persistent large varices, 4 of which were noted to be thrombosed. Thus 9/16 (53.1 %) of patients in NBC group met the study objective.

DISCUSSION: This is the first study which demonstrates the efficacy of thrombin - fibrin glue along with sclerosant as a mode of endotherapy of gastric varices. Thrombin glue, besides being highly efficacious in causing blood coagulation in the gastric varices has a number of potential advantages:

1) It is derived from human plasma.
2) The efficacy of thrombin in causing blood coagulation has been extensively studied and its effect on blood coagulation is predictable. Till date thrombin has ubiquitous uses in vascular surgery and neurosurgery.
3) There is virtually no chance of damage to the endoscope.
4) Cast extrusion, which is a late complication of NBC, and a potential cause of rebleed from the gastric varices is not a problem with thrombin based glue.

As thrombin based glues are derived from human plasma, some theoretical risk of infection with blood borne viruses is present. However as most of the manufacturers are strictly following (Committee for Proprietary Medicinal products) guidelines, the risk is negligible. As the results of the present study are highly encouraging, further studies to compare the efficacy of TFG/S with NBC in a randomized fashion needs to be planned. The results of the present study need to be confirmed in a multicentric setting also.

Therapy with TFG/S is a highly versatile therapy for the management of portal hypertensive bleed. Besides gastric varices, we have so far treated with excellent results four patients with bleeds from large rectal varices, two patients with advanced liver disease and massive bleeds from large internal hemorrhoids, and one patient with bleeding esophageal varices, uncontrolled with EST alone.

One session of therapy with TFG/S costs approximately Rs. 7500 ($125) as compared to Rs. 3, 000 to Rs. 4, 500 ($ 45 -75) with NBC. Although the cost per session with TFG/S is approx. two times as compared with NBC, the high initial costs are offset by low rates of rebleeds, decreased need for hospitalization due to bleeds and virtual no risk of damage to the endoscope.
CONCLUSION: The optimal management of bleeding gastric varices remains to be standardized. Although tissue adhesives like NBC remains the most preferred therapy, the results with thrombin/fibrin glue and sclerotherapy are highly encouraging, and compares favorably or even better than NBC. Well-designed trials therefore need to be performed to evaluate its efficacy.

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