

THE INCIDENCE AND OCCURRENCE OF GASTROESOPHAGEAL AND FUNDAL VARICES IN PATIENTS WITH PORTAL HYPERTENSIVE BLEEDING AND THE SAFETY OF USING HISTO-ACRYL GLUE. A PROSPECTIVE COHORT STUDY

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Abstract:

Introduction: Variceal bleeding is a frequent and life-threatening complication of portal hypertension. The first episode of variceal bleeding is associated not only with a high mortality, but also with a high recurrence rate in those who survive.

Aims: Assess the incidence of presence of GOV or IGV during the primary event of bleeding from portal hypertension. The development of GOV and or IGV in cases with bleeding from portal hypertension later during the course of endoscopic treatment that was not present at the initial endoscopy. Safety of using HA in the management of GOV / IGV.

Methods: A prospective randomized cohort study was conducted over a period of 7 years, 2014 patients who presented with with variceal bleeding. Patients were randomly divided into 2 groups; group 1 was managed by band ligation (BL) for esophageal varices(EV) & group 2 was managed by injection sclerotherapy (using ethanolamine sclerosant material).

Results: All the patients included in the study presented with gastrointestinal bleeding who were selected randomly and these were 2014 patients in total.

Discussion: The incidence of developing fundal varices which were originally not present with the management of the esophageal varices is 60% with having a bleeding incidence of 60% being more with band ligation than with sclerotherapy, this necessitates close follow up even after the obliteration of esophageal varices, at least for 3 months after obliteration of the esophageal varices. To our opinion the use of cyanoacrylate for the management of fundal varices is a safe and effective method to endoscopically control bleeding from fundal varices.

{**Citation:** Safwat W, Amgad Anas, Ahmad Gamal, Mohamed Abou El EZZ, Mohamed Darwish El Talkawy, Mohy Eldeen Attayia. The incidence and occurrence of gastroesophageal and fundal varices in patients with portal hypertensive bleeding and the safety of using histoacryl glue: a prospective cohort study. American Journal of Research Communication, 2016, 4(9): 18-27} www.usa-journals.com, ISSN: 2325-4076.

Introduction

Variceal bleeding is a frequent and life-threatening complication of portal hypertension. The first episode of variceal bleeding is associated not only with a high mortality, but also with a high recurrence rate in those who survive. Therefore, management should focus on different therapeutic strategies aiming to prevent the first episode of variceal bleeding (primary prophylaxis), to control hemorrhage during the acute bleeding episode (emergency treatment), and to prevent re-bleeding (secondary prophylaxis). These strategies involve pharmacological, endoscopic, surgical, and interventional radiological modalities ^[1]. Bleeding from esophageal varices (EVs) or gastric varices (GVs) is a catastrophic complication of chronic liver disease. Bleeding from GVVs is generally thought to be more severe than bleeding from EVs, but it occurs less frequently ^[2,3]. Many recent developments have improved the outcome of treatments for GVVs. The red color sign is an elevated red area which has proven to be important in portending variceal bleeding. The histological manifestation is a thinning of the epithelial layer. The North Italian Endoscopic Club for the Study and Treatment of Esophageal varices ^[9] published a report establishing that the red color sign on EVs is predictive of bleeding. It remains unclear whether the endoscopic red color sign in the stomach has the same significance as the red color sign in the esophagus. In the latter case does it denote a thinning of the epithelial layer. The varix in the submucosa of the stomach is covered by the muscularis mucosae and propria mucosae. This generally confers an appearance different from that typical of the thinning epithelial layer of the esophagus ^[7]. The gastroesophageal varices are important because of their propensity to bleed ^[8]. Acute bleeding from gastric varices can be massive and fatal. As there are relatively few randomized controlled trials investigating the relative efficacy of various treatment modalities, the management of gastric variceal bleeding is controversial and varies from center to center ^[1]. Non-endoscopic methods, such as transjugular intrahepatic portosystemic shunt (TIPS) and

surgical portosystemic shunts are effective but require experienced specialists. Moreover emergency shunt carries a high rate of post operative mortality. The discovery of tissue adhesive chemical has changed the management of gastric variceal bleeding. N-Butyl Cyanoacrylate (Histoacryl™), a tissue adhesive, was first applied for endoscopic treatment of bleeding GVs in 1980s. Thereafter, cyanoacrylate has become popular for this purpose in many countries^[9].

Aims

1-Assess the incidence of presence of GOV or IGV during the primary event of bleeding from portal hypertension.

2-The development of GOV and or IGV in cases with bleeding from portal hypertension later during the course of endoscopic treatment that was not present at the initial endoscopy.

3-Safety of using HA in the management of GOV / IGV.

Methods

A prospective randomized cohort study was conducted over a period of 7 years, 2014 patients who presented with with variceal bleeding. Patients were randomly divided into 2 groups; group 1 was managed by band ligation (BL) for esophageal varices(EV) & group 2 was managed by injection sclerotherapy (using ethanolamine sclerosant material). Patients with HCC were managed by injection sclerotherapy for the EV. GOV / IGV were injected using HA. Patients underwent endoscopy after initial resuscitation and proper gastric wash. Patients assumed the regular left lateral position, but whenever there was a problem with blood in the fundus due to non-stop bleeding or re-bleeding during the procedure and the blood made it difficult to see the fundus sometimes the patient was put on the right lateral position if suction through the endoscope was not enough to get out the blood. Commercially flexible sclerotherapy injectors, 21-gauge needle were used for gastric variceal injection. N-butyl-2-cyanoacrylate (Histoacryl™), was mixed with Lipidol™ Lipidol was used to flush the needle before and after each injection. All injections were directly delivered into gastric varices with active bleeding or containing stigmata of recent bleeding. At two week-follow-up endoscopy, reinjection was

performed, if GVs were still detectable by palpation with the tip of the sheath of the needle. If there was recurrent bleeding during the follow-up period, reinjection with cyanoacrylate was performed again. Follow up endoscopy was performed in all the patients every two weeks and were followed up for a minimum of 3 months. Initial success was defined as an absence of recurrent bleeding after the first cyanoacrylate injection and during the follow-up period. Secondary success was defined as an absence of recurrent bleeding after reinjection of cyanoacrylate for recurrent bleeding and treatment failure is defined as not being not able to stop bleeding endoscopically after multiple re-bleeds. The gastric varices or Fundal varices (FV) were classified as Gastroesophageal varices and isolated gastric varices mostly complies with the classification proposed by Sarin *et al.*^[10] in which gastric varices were classified by their location: varices in the esophagus and lesser curvature (GOV1); varices in the esophagus and gastric fundus (GOV2); varices in the fundus only (IGV1); or varices at other sites in the stomach or in the first part of the duodenum (IGV2).

Results

All the patients included in the study presented with gastrointestinal bleeding who were selected randomly and these were 2014 patients in total. The primary endoscopic findings are shown in (Table1).

Table 1. Primary endoscopic findings at first endoscopy

Primary endoscopic findings at first endoscopy		
	Number of patients	% of patients
Esophageal varices	1325	65.8%
Combined esophageal varices with gastric extensions(GOV) 1 & 2	530	26.3%
Isolated GOV 1&2 with no esophageal varices or isolated gastric varices (IGV1)	159	7.9%
IGV 2	Zero	0%

The primary bleeding source which was identified either by the presence of active bleeding or signs of recent bleeding and are shown in (Table 2). These figures were calculated from the total amount of the studied population.

Table 2. Identified bleeding source

Identified bleeding source		
	Number of patients	% of patients
EV	1537	76.3%
GOV, IGV 1	424	21.1%
EV + GOV	53	2.6%

Group 1 included 751 patients & underwent BL, group 2 included 733 patients underwent injection sclerotherapy using EAO. Patients with HCC 371 patients were all injected using EAO for OV. Histoacryl was used in 1484 patients only for the injection of fundal varices. The incidence of development of GOV which were not initially present and developed after management of EV (1325 patients), 795 patients(60%) developed secondary FV from which (60%) bleed; (74.2%) post band and (25.8%) post injection sclerotherapy (during the first 3 months). In the 530 patients with combined OV & FV (60%) patients had primarily bleeding from the FV and (10%) patients had combined bleeding from both OV & FV, the remaining 159(30%) patients underwent treatment only for the OV from which 127 (79.8%) patients had bleeding from the FV within the first 3 month. Histo-acryl glue injection used in 1484 patients stopped bleeding from fundal varices in 1-3 sessions, achieving secondary success and there was no treatment failures. Complications in the studied population occurred in 85 patients (5.7%). In the form of; 2 (0.14%) patients died from pulmonary embolism, 66 (4.5%) patients had fever as a form of a reaction which all subsided and 17 (1.15%) patients had ulcers due to false injection in a fold healed in a period from 6 weeks up to 10 month with no significant bleeds.

Discussion

Portal hypertension, the main complication of cirrhosis, is responsible for variceal hemorrhage, ascites, and portosystemic encephalopathy. Of these complications, variceal

bleeding is a frequent and life-threatening complication. Gastric varices are abnormally dilated submucosal veins in the stomach that can be a life-threatening cause of upper GI hemorrhage. Gastric varices are caused most commonly by, cirrhosis with associated portal hypertension. The first episode of variceal bleeding is associated not only with a high mortality, but also with a high recurrence rate in those who survive. Portal vein thrombosis can cause gastric varices, and there have been several reports of gastric varices developing after endoscopic therapy for bleeding esophageal varices^[11] In our large prospective randomized trial, the overall incidence of gastric varices in cases which presented with active bleeding due to portal hypertension was 34.2%, but with an incidence of being the bleeding source in 23.7% of all cases of portal hypertensive bleeding, these figures are consistent with Sarin et al. and Ryan et al. ^{[11] [12]}, this is definitely more than earlier reports that may have had smaller sample size, more over in cases who harbor both esophageal and fundal varices at the time of bleeding the source of bleeding was from fundal varices in 60% of cases, this figure is slightly higher from other reports. The incidence of bleeding in cases with fundal varices is 69% this is very different from the figures reported by Mumtaz et al.,^[17] who reported that fundal varices can be seen in 15% of patients with portal hypertension and the incidence of bleeding is 22.7%. Moreover non of the reports mentioned that the bleeding site could be combined from both fundal and esophageal varices, which we were able to detect in 53 patients (10%). The management of esophageal varices by injection sclerotherapy in cases with known HCC was utilized due to higher incidence of re-bleeding due to probable portal vein thrombosis and lower healing rates which is usually more severe with band ligation than that with sclerotherapy, this data is consistent with Phadet Noophun *et al.*, who stated in their study that HCC was found more often in failure group of management of varices (6 of 7 patients) compared to success group (1 of 17 patients)^[13]. The fact that newly developing fundal varices during the course of management of esophageal varices occurred in 60% of cases which is consistent with Yüksel O et al., ^[14] however our data differs with this study that the incidence of bleeding from these newly developed was studied during follow up and was found to be in 60% of these cases with a much higher incidence post band ligation (74.2%) versus (25.8%) post injection sclerotherapy while it was the same for the two methods of treatment in the other study. This finding of increased incidence of fundal varices which is more after band ligation than after sclerotherapy is consistent with Shahid S. et al., ^[15]. The cases which presents with bleeding esophageal varices but in the same time have fundal varices is currently in many centers managed by only injecting the bleeding source which would be the esophageal varices,

but owing to the previous findings from which we would assume that the treatment of esophageal varices would lead to propagated pressure to the stomach and fundal varices^[14-16]. In our study we came with the finding that the management of esophageal varices in the presence of fundal varices would lead to a 79.8% chance of having these fundal varices bleeding within 3 months from the primary bleed, that would lead to an important recommendation of the importance of treatment of fundal varices, if present, in the same session or shortly after in cases of bleeding esophageal varices. Management of fundal varices could be challenging with many proposed lines of treatment; endoscopic, radiological and surgical. Except for the endoscopic line of treatment which provides a line for diagnosis initially and also for follow up and we see that this is the best modality of treatment with safe and effective outcomes in the right experienced hands. Compared with endoscopic sclerotherapy or band ligation, endoscopic variceal occlusion with tissue adhesive such as N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin is more effective for acute fundal gastric variceal bleeding. Successful obliteration leads to both better control of initial hemorrhage and lower rebleeding rates^{[18], [19]}. A relatively large prospective randomized trial compared gastric variceal occlusion with N-butyl-cyanoacrylate versus band ligation in patients with acute gastric variceal hemorrhage, demonstrating that control of active bleeding was similar in both groups but that rebleeding over a follow-up period of 1.6 to 1.8 years occurred significantly less frequently in the N-butyl-cyanoacrylate group (23% versus 47%), with an average of only 1.5 sessions (range 1 to 3)^[20]. Therefore, the use of these agents is preferred. Earlier report by Sohendra et al.^[23], has stated that the endoscopic hemostasis of severe variceal bleedings has become safer and surer. The overall hospital mortality of these patients has sunk from 31.5 to 17.5% in their series. Cyanoacrylate is a very useful substance for obliterating large esophagogastric varices. In our study all the 1484 case which initially had or developed fundal varices were managed endoscopically using N-butyl-cyanoacrylate with 100% success in controlling bleeding within 1-3 sessions of sclerotherapy. This is consistent with Mumtaz et al.^[17], None of the patients in the studied group had mortality from uncontrolled bleeding; endoscopic treatment was able to stop bleeding in all patients. When injected intravascularly, N-butyl-2-cyanoacrylate promptly solidifies, producing a cast of the vessel. Subtotal occlusion is immediate, and total occlusion occurs within hours^[21,22]. In variceal applications, the cast of glue extrudes into the lumen after a week or two, generally without resultant bleeding. Complications that occurred in (5.7%). In the form of; 2 (0.14%) patients died from pulmonary embolism, which is rather considered an extremely low rate as compared to

other studies with low number of studied patients as this study which had 2 patients with embolic complications but the overall number studied was 24 patients, however the patient who had pulmonary embolism fortunately survived the incident with conservative management^[13]. Sixty six (4.5%) patients had fever as a form of a reaction which all subsided, all patients had prophylactic antibiotic coverage after the procedure. Gastric varices are sometimes difficult to detect by endoscopy and are often are mistaken for a mucosal fold^[11]. Endoscopy for evaluation of gastric varices had a sensitivity of 48% and a specificity of 50%^[24]. In our study, actually the opposite of missing fundal varices and due to the difficulty of sometimes differentiating fundal varices from large, congested and edematous gastric folds, we had 17 (1.15%) patients had ulcers due to false injection in a fold healed in a period from 6 weeks up to 10 month with no significant bleeds. So as to come to a conclusion to our study; the incidence of having bleeding from fundal varices is 23.7%. In case of the presence of combined esophageal and fundal varices, the management of esophageal varices will lead to a 79.8% incidence of bleeding from the fundal varices within the first 3 months. This makes it important to treat both esophageal and fundal varices in the same session or shortly after. The incidence of developing fundal varices which were originally not present with the management of the esophageal varices is 60% with having a bleeding incidence of 60% being more with band ligation than with sclerotherapy, this necessitates close follow up even after the obliteration of esophageal varices, at least for 3 months after obliteration of the esophageal varices. To our opinion the use of cyanoacrylate for the management of fundal varices is a safe and effective method to endoscopically control bleeding from fundal varices.

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