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Hemostatic Powder for Management of Acute Variceal Bleeding

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Abstract

Background: Acute variceal bleeding (AVB) is a potentially fatal complication in cirrhotic patients with portal hypertension. Simple endoscopic techniques requiring limited expertise are needed to improve morbidity and mortality.

Aim of Study: To test the efficacy of hemostatic powder for control of AVB due to portal hypertension in cirrhotic patients presenting in the emergency department.

Patients and Methods: In this single-arm, prospective study, conducted at a center in Egypt, patients admitted to the emergency department with suspected AVB were admitted. Endoscopy was performed within 6 hours of admission and hemostatic powder was applied in the case variceal bleeding was performed. Patients were observed for 24 hours and underwent second endoscopy and definitive therapy the following day.

Results: Forty patients were admitted and after the first endoscopy, 32 had confirmed AVB. Child-Pugh class C liver disease was present in 50% of patients. Esophageal varices were observed in 78.1% of patients, gastric varices in 12.5% and duodenal varices in 9.4%. No major adverse events or mortalities were observed during the follow-up. All patients achieved primary endoscopic hemostasis.

Conclusion: In cirrhotic patients presenting to the emergency department with suspected AVB, hemostatic powder application was safe and effective for achieving endoscopic hemostasis.

Key Words: *Liver cirrhosis – Hemospray – Variceal bleeding.*

Introduction

PORTAL hypertension is a complication of liver cirrhosis that results in elevated portosystemic collateral flow especially in the mucosa of the proximal stomach and the distal esophagus **[1]**. As a result, gastroesophageal varices may develop which are at risk of rupturing and potentially fatal bleeding. Esophageal varices are present in 40-70% of patients with cirrhosis with mortality reaching 20% with the main cause for death within the first 5 days being blood loss **[2,3]**.

Endoscopy is the gold standard for treatment of acute variceal bleeding (AVB). Guidelines suggest additional support with restricted blood transfusion approach (to achieve 7-8g/dL hemoglobin), vasoactive drugs and antibiotics prior to endoscopic therapy. The latter consists of variceal band ligation of esophageal varices and obturation of gastric varices with cyanoacrylate injection **[4]**.

Timing of endoscopy in AVB patients has been debatable with guidelines suggesting early treatment within 24 hours of admission **[4]**. Recently, in a systematic review conducted by Bai et al., on cirrhotic patients with acute variceal bleeding, overall mortality was significantly lower in early endoscopy group (<12h) than the delayed endoscopy group (>12h) **[5]**. While there is still a lot of debate regarding this issue, it is clear that ensuring hemodynamic stability of the patient as soon as possible as well as considering the resources available in the endoscopic unit are key.

Hemospray® (COOK Endoscopy, Winston Salem, NC, USA) is a novel hemostatic powder, also known as hemostastic powder TC-325, that is licensed for endoscopic hemostasis of non-variceal upper gastrointestinal (GI) bleeding. Preliminary studies proved that it was effective in patients with peptic ulcer bleeding with a variety of studies exploring Hemospray® use in patients with variceal bleeding **[6-8]**. Such treatment does not require technical expertise as the powder is delivered during withdrawal of the scope from the cardia to mid-third of the esophagus.

In this prospective study, we evaluated the safety and effectiveness of Hemospray® application for control of variceal bleeding in cirrhotic patients presenting in the emergency department.

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Material and Methods

This prospective, single-arm study was conducted on 40 patients who were admitted to the hospital and endoscopy center presenting with hematemesis and/or melena with known or suspected liver cirrhosis between March 2019 and July 2019. All patients signed a consent form prior to inclusion in the study. Eligible patients were those who were 18 years or older with endoscopic confirmation of AVB. Endoscopic confirmation of AVB was defined as active bleeding or fresh blood in the stomach with signs on the varices with no other cause of bleeding. Exclusion criteria included inability to consent, any contraindications to undergoing endoscopy, pregnant or lactation patients, patients with non-variceal causes of bleeding at the time of endoscopy, patients with previously placed intra-hepatic portosystemic shunt and patients who in the 30 days prior to intended. Hemospray® application has been treated with any other endoscopic or surgical modalities.

The device used for the application of the powder in seen in Fig. (1). It consists of an application catheter that can be passed through the working channel of a therapeutic gastroscope, a chamber containing about 21g of hemostatic powder as well as a propellant CO2 canister. The powder works by increasing the concentration of clotting factors, activating platelets, and forming a mechanical plug on a bleeding vessel. When in contact with the moisture in the gastrointestinal tract, the powder then becomes cohesive and adhesive, forming a stable barrier that covers the bleeding site. The powder is not absorbed or metabolized by mucosal tissue, eliminating the risk of systemic toxicity. The powder covering the mucosa then separates from the wall and is eliminated naturally from the gastrointestinal tract.

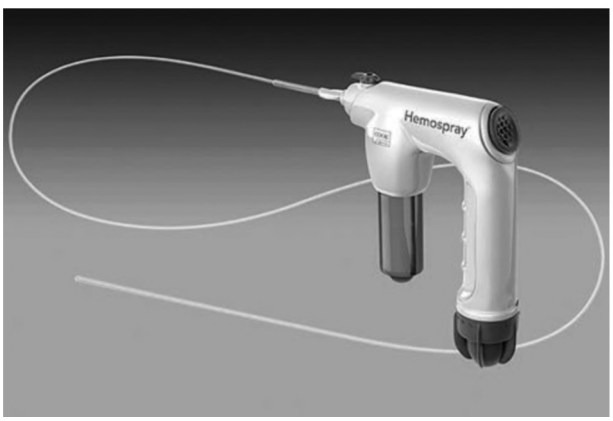

Fig. (1): Hemospray® device.

In all included patients, urgent hemodynamic stabilization was performed by providing octreotide (50mcg bolus at admission and then 25mcg/hour for 24 hours) and intravenous ceftriaxone (1g/24 hours). All patients received endoscopy within six hours of admission. Upon confirmation of active variceal bleeding, Hemospray® was applied. After confirmation of AVB, a bleeding site was defined as the most probable source with the hemostatic powder being administered in a diffuse fashion to cover the mucosa completely, obtaining immediate endoscopic hemostasis. For esophageal varices, the catheter was positioned at the level of the cardia in the center of the lumen with the power being applied as the endoscope was pulled backwards over an area of about 12-15cm of the distal esophagus. Upon the first application of the powder, the bleeding site was observed for three minutes. In case of bleeding recurrence, Hemospray® was reapplied until hemostasis was achieved.

Following endoscopy, patients were monitored for 24 hours with continuous infusion of octreotide (25mcg/hour) and institutional standard of card. Definitive therapy was performed endoscopically the next day consisting of band ligation for esophageal varices and/or cyanoacrylate injection for gastric varices. All patients were then followed up for five days which is the period of the acute bleeding episode.

The primary outcomes of the study include endoscopic and clinical hemostasis achieved by Hemospray®. Endoscopic hemostasis which was defined as the absence of fresh hematemesis within two hours after the application of the powder as well as lack of hemoglobin drop of 3g/dl without blood transfusion. Clinical hemostasis was defined as the absence of a single episode of clinically significant rebleeding within 24 hours after the application of the hemostatic powder.

Analysis was performed using SPSS 27.0.0 (SPSS Inc, Chicago, Il, USA). Data were expressed as percentages, means, standard deviations (SD) or medians and ranges, as appropriate.

Results

Forty consecutive patients with liver disease and suspected AVB were included. Eight patients were excluded due to non-variceal bleeding etiologies (Fig. 2). The mean age of the 32 patients was 62.3 years (range 35-74) with 23 males (71.8%). All patients were classified as post-hepatitis C cirrhotic patients with 16 (50.0%) of the patients having Child-Pugh's classification C. Baseline demographics of the patients are summarized in Table (1).

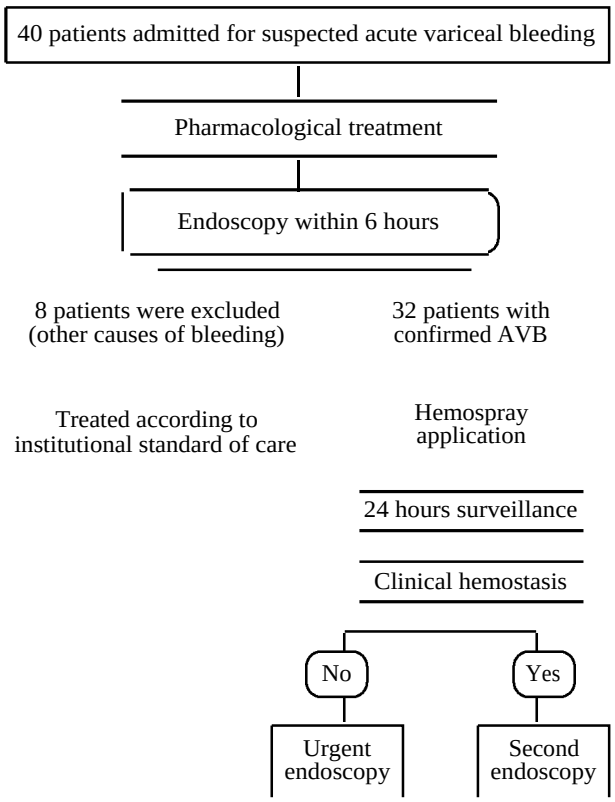

Fig. (2): Flowchart depicting the study design.

Table (1): Baseline demographics of patients*.

Age (year)	62 (35-74)
Sex (M/F)	23 (71.8%)/9 (28.2%)
Child-Pugh's classification (CHILD A/CHILD B/ CHILD C)	3 (9%)/13 (41%)/16 (50%)
Clinical presentation at admission	Hematemesis: 18 (56.25%) Melena: 6 (18.75%) Hematemesis and melena: 8 (25%)

*Data are expressed as medians for continuous variables and as members (percentages) for categorical variables.
M: Male. F: Female.

Endoscopy was performed under sedation without endotracheal intubation. Bleeding originated from esophageal varices in 78.1% patients, from gastric varices in 12.5% and 9.4% from duodenal varices. Spurting bleeding, defined as actively bleeding varices at the time of endoscopy, was observed in 13/32 (40.6%) and acute bleeding, defined as presence fibrin plugs and/or red streaks of the mucosa overlying the varices with presence of fresh blood within the lumen, in 17/32 (53.1%).

Primary endoscopic hemostasis, defined as immediate hemostasis after the application of the powder, was achieved in all patients at the time of Hemospray® application using one device in 31 patients and two devices in one patient. All patients were O2 saturation monitored for 24 hours with no clinical signs of pulmonary embolism observed. Clinical hemostasis, as defined above, was achieved in 30/32 (93.75%) patients during the next 24 hours after powder application. No patients experienced hematemesis after Hemospray® application. At follow-up endoscopy, hemostatic powder was completely eliminated from the upper GI tract in 30/32 (93.75%) patients and endoscopic hemostasis was achieved in all patients. No major adverse events (e.g. embolization, bowel obstruction, allergic reaction) were observed. Although all patients were treated with sedation without endotracheal intubation, no patients experienced inhalation pneumonia. No mortalities were reported during 15 days' follow-up. An elective band ligation was performed in patients with esophageal varices and cyanoacrylate injection in patients with gastric varices at the time of second endoscopy, while the three patients with duodenal varices were treated with beta blockers and were followed-up for three months without further bleeding.

Discussion

This prospective study showcases the effectiveness of the application of a hemostatic powder in controlling bleeding and stabilization of patients that present with AVB. This allows for patients to be stabilized until endoscopy can be performed to allow for additional definitive therapy under optimal, non-emergency conditions.

The earliest reports of Hemospray use in AVB consist of two case reports **[9,10]**. Both patients presented with gastric fundal variceal bleeding refractory to standard endoscopic therapy. In both cases, the varices were injected with Histoacryl and Lipiodol without achieving hemostasis. Hemospray was applied in these cases resulting in immediate hemostasis. Neither of the cases reported any complications or embolization of the powder.

Hagel et al., explored the efficacy of Hemospray in gastrointestinal bleeding during emergency endoscopy. Of 27 patients, only two were reported to have esophageal variceal bleeding and Hemospray was applied as a salvage therapy after variceal ligature was conducted as first line therapy. In both patients, Hemospray achieved hemostasis both immediately and permanently **[11]**. The research group consisting of Ibrahim et al., conducted two main studies focused on the management of acute variceal bleeding using Hemospray as a first modality **[12,13]**. The first study consisted of a pilot study on nine patients with confirmed AVB who

underwent treatment within 12 hours of hospital admission. For each of the patients, hemostatic powder was applied once or twice (at about 3 minutes apart) to achieve immediate hemostasis. In eight of the patients, only one application was necessary to achieve hemostasis. On follow-up endoscopy, no patients had any active bleeding. For the second study, a randomized trial was conducted comparing the outcomes of patients with AVB who underwent immediate endoscopy with hemostatic powder within 2 hours of admission followed by elective endoscopy the next day (within 12-24 hours of admission) versus patients who only underwent elective endoscopy. In the study group, five out of 39 patients with successful Hemospray application had rebleeding within the first 12 hours, yet none had rebleeding later after elective endoscopy within the first 5 days **[12]**. In a recent systematic review and meta-analysis on the efficacy of Hemospray in upper gastrointestinal bleeding, the aforementioned studies were analyzed and it was concluded that in patients with variceal bleeding, immediate hemostasis was achieved in 92.7% ($p<.001$) of patients, with a rebleeding rate of 2.1% ($p<.001$) **[8]**. These results are in line with our current study in which primary endoscopic hemostasis was achieved in all of the patients without any adverse effects.

Hemospray, in its simplicity, could reduce the proportion of delayed endoscopies. This might equalize the results of immediate hemostasis and provide an opportunity for patients to be treated, once their condition has stabilized, by the most experienced endoscopist. The benefits include achievement of immediate hemostasis using a simple, minimally operator dependent technique.

In conclusion, management of AVB using hemostatic powder is feasible and safe by offering immediate hemostasis using a minimally operator-dependent technique. Further multi-center studies comparing the long-term effects of the technique as well as its feasibility in resource-deficient centers are needed.

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بوردة هموسبراى لعلاج نزيف الدوالى الحاد

\الخلفية: نزيف الدوالى الحاد هو مضاعفات قاتلة فى مرضى التليف الكبدى مع ارتفاع ضغط الدم البابى. يجب إيجاد تقنيات التنظير البسيطة التى تتطلب خبرة محدودة مطلوبة لتحسين معدلات الاعتلال والوفيات.

هدف \الدراسة: لاختبار فعالية هيموسبراى على نزيف الدوالى الحاد بسبب ارتفاع ضغط الدم البابى فى مرضى التليف الكبدى الموجودين فى قسم الطوارئ.

\المرضى: فى هذه الدراسة الاستباقية أحادية الذراع التى أجريت فى مركز فى مصر، تم قبول المرضى الذين تم إدخالهم إلى قسم الطوارئ مع الاشتباه فى نزيف الدوالى الحاد. تم إجراء التنظير فى غضون ٦ ساعات من القبول وتم تطبيق مسحوق الهيموسبراى فى حالة إجراء نزيف الدوالى. تمت مراقبة المرضى لمدة ساعة وخضعوا للتنظير الثانى والعلاج النهائى فى اليوم التالى.

\النتائج: تم قبول أربعين مريضاً وبعد التنظير الأول، أكد وجود نزيف الدوالى الحاد فى ٢٢ مريضاً AVB. كان مرضى تليف الكبد من C Child-Pugh موجوداً فى ٥٠٪ من المرضى. لوحظت دوالى المرئ فى ٧٨.١٪ من المرضى، دوالى المعدة فى ١٢.٥٪ ودوالى الاثنى عشر فى ٩.٤٪. لم يلاحظ أى أحداث سلبية أو وفيات أثناء المتابعة. تم إيقاف النزيف فى حقق جميع المرضى.

\الاستنتاج: فى مرضى التليف الكبدى الذين يتقدمون إلى قسم الطوارئ مع الاشتباه فى نزيف الدوالى الحاد، كان تطبيق مسحوق الهيموسبراى آمناً وفعالاً لتحقيق الإرقاء بالمنظار.