Controlling gastric variceal bleeding with endoscopically applied hemostatic powder (Hemospray™)

To the Editor:
Gastric variceal bleeding tends to be more severe (2.9 vs. 4.8 transfusion units per patient) and is associated with a higher mortality (30% vs. 45%) than bleeding from oesophageal varices [1–3].

Failure of endoscopic therapy commonly requires rescue placement of a transjugular intrahepatic portosystemic shunt (TIPS) [4], but this option is costly and not always feasible.

Hemospray™ is a novel hemostatic spray recently introduced for the management of non-variceal upper gastrointestinal bleeding [5].

We describe the first case of variceal bleeding refractory to standard endoscopic therapy, successfully treated with Hemospray™, obviating the need for TIPS.

A 79-year-old woman presented to the emergency department with a 3-day history of melena. Her previous medical history included idiopathic myelofibrosis with hepatosplenomegaly due to extramedullary hematopoiesis. This was complicated by portal hypertension and ascites. Furthermore, she suffered from a severe hypertension-related pre-existent dilated cardiomyopathy. Previous upper endoscopy did not show the presence of varices.

At presentation she had a blood pressure of 80/40 mmHg with a pulse rate of 90 bpm with peripheral cyanosis. On rectal examination, black stools were noticed. Laboratory test results showed haemoglobin 4.8 mmol/L, urea 27 mmol/L, creatinine 68 mmol/L, INR 1.4, and normal transaminases and bilirubin.

In anticipation of a variceal haemorrhage, standard administration of an antibiotic (norfloxacin 400 mg twice daily) and vasopressor drugs (octreotide) was initiated. Fluid and packed cell administration was restricted to stabilize vital signs. The patient was intubated and transferred to the intensive care unit.

Upper gastrointestinal endoscopy was performed using an Olympus Q180-1T scope (Olympus, Japan). In the distal esophagus, small varices without bleeding stigmata were seen, but in the gastric fundus, a profusely bleeding varix of 8 mm (GOV2) was observed. Next, in three consecutive injections, a total volume of 2.6 ml HistoAcryl™ with lipiodol was injected. However, hemostasis could not be achieved and hemodynamic instability ensued. Rescue treatment with TIPS was considered, but not pursued given her cardiac condition. Instead of injecting more HistoAcryl™, we decided to apply Hemospray™ (Cook Medical, USA). For this, we sprayed approximately 10 g of Hemospray™ covering the entire bleeding varix. Persistent hemostasis was confirmed after 5 min of visual inspection.

The patient received standard post-endoscopic care and went home. No rebleeding occurred at follow-up at day 7 and 30. We did not perform a second-look endoscopy given the absence of signs of rebleeding.

Gastric variceal haemorrhage is an acute life-threatening condition in which the endoscopist is challenged to act swiftly in a technically demanding retroflexed position. Endoscopic management involves single or multiple injection(s) of cyanoacrylate glue into the varix resulting in the formation of a polymeric plug. Despite its relative high initial hemostasis rate (87–100%) [1], injection carries distinct risks. First, polymerisation of acrylate beyond the bleeding site may result in thromboembolic events [1]. Second, needle obstruction frequently occurs necessitating retrieval. This means loss of precious time. Third, ulceration of the bleeding site after injection is commonly seen, and may result in secondary bleeding [1].

When hemostatic treatment with cyanoacrylate glue fails, urgent TIPS is not always feasible due to local unavailability, when the patient condition is too unstable or, as in this case, when there are clear contraindications such as cardiomyopathy [6].

Hemospray™ is a novel proprietary hemostatic spray recently introduced for the management of non-variceal upper gastrointestinal bleeding. Its safety and efficacy have been shown in peptic ulcer bleeding [5], as well as in cancer-related upper GI bleeding [7]. Upon application, this inorganic hemostatic powder becomes cohesive and adhesive, and forms a stable mechanical barrier that covers the bleeding site. We report on the first case in literature in which Hemospray™ is successfully applied in initially failed endoscopic hemostasis of a variceal bleeding.

There are few concerns that need to be addressed. Hemospray™ is applied by a CO₂-propelled canister with a positive outflow pressure. Hypothetically, particles may enter the vascular system and give rise to venous thromboembolisation. However, the outflow pressure at the catheter tip is less than the known intravascular venous pressures (often exceeding 15 mmHg) [8] at a distance of 1–2 cm from the mucosa. Also, data from an ongoing multicentre European initiative on the use of Hemospray™ for non-variceal upper GI bleeding does not report incidence of thromboembolism (unpublished data). Another concern involves the effects of Hemospray™ in coagulation. This is important since most gastric varices occur in cirrhotic patients with frequent unbalance of pro- and anticoagulatory factors [9]. More studies need to be performed to elucidate this issue, but preliminary data show only minor in vitro effects of Hemospray™ on coagulation parameters [10].

In conclusion, Hemospray™ may offer a simple and welcome alternative in durably controlling bleeding (gastric) varices. However, we need to await its use in controlled trials to determine the true added value.

Conflict of interest

J.W.P. is consultant for Cook Medical. The other authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.
Letters to the Editor

Other disclosures

The use of Hemospray™ for variceal bleeding is currently not an indicated use in the device labelling.

References


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T regulatory cell number and function: The autoimmune traits in liver diseases

To the Editor: We read with great interest a recent article published in this journal by Peiseler et al. [1], together with the accompanying editorial [2], regarding the T regulatory cells (Tregs) in autoimmune hepatitis (AIH). Peiseler et al. found that CD4+CD25high CD127lowFOXP3+ Tregs in AIH are “fully functional and not reduced in frequency”. Longhi et al. [3], who had previously published that Tregs are functionally impaired in AIH, first argued against the methodology used for assessing the Tregs suppressor activity, since Peiseler et al. employed an “utterly non-physiological” suppressor/effector ratio. Peiseler et al. replied by stating that their methodology for staining proliferating cells by carboxyfluorescein succinimidyl ester (CFSE) is more appropriate than thymidine uptake and specifically stains the CD4+CD25+ effector T cells.

Another argument was raised regarding the choice of the Tregs labeling gate that resulted in a lower Tregs frequency compared with that reported by others [4]. The authors replied [5] by stating that the frequency of peripheral blood Tregs in adults reported by Garg et al. is “not vastly different from the frequencies reported by us”. Garg et al. [4] extrapolated that the Tregs number from CD4+CD25high-labeled cells, considering only the top 1% of CD25-staining CD4 T cells, as being estimated to be >98% CD127low. We believe that the comparison of Tregs frequencies is questionable and age-related, as demonstrated by our data. Peripheral blood cells from 4 healthy, 4 AIH, and 4 non-alcoholic steatohepatitis (NASH) children (age range: 10–14 years) were used to evaluate frequencies of CD4+CD25highCD127lowFOXP3+ Tregs (Fig. 1A–C). As reported in Fig. 1D, the number of CD25highCD127lowFOXP3+ Tregs within the CD4+ population is equal in all the groups of children. Our data confirms that the number of CD4+CD25highCD127low “True” Tregs remains unchanged in liver disease with autoimmune traits, including AIH and NASH as already reported [1,6]. However, in children, the number of CD25lowCD127lowFOXP3+ Tregs among CD4+ ranges from between 2.3% and 3.0%. In summary, all of these findings highlight the importance of a “consensus” in the standardization of protocols for evaluating the Tregs function in AIH and NASH.

In addition, we would raise a discussion concerning some aspects related to non-alcoholic steatohepatitis (NASH). Peiseler et al. determined the intra-hepatic Tregs frequency by immunohistochemistry for FOXP3 in 8 NASH patients, in comparison to AIH [1], and found a higher percentage of FOXP3+ cells in AIH patients when compared to NASH subjects, both in liver lobules and in portal tracts. Moreover, they determined that the FOXP3+ cells within the CD3+ population in the liver showed no statistical differences between AIH and NASH patients. No information about the diagnosis and severity of NASH was provided by the authors. Further, the usage of the modified histological activity index (mHAI) [7], for quantifying the degree of liver inflammation, is not suitable for NASH patients who are histologically evaluated by using the NAFLD Clinical Research Network criteria [8]. As liver-resident inflammatory cells are a key component in NAFLD, particularly in children [9], their role in the severity of NASH-associated necroinflammation and fibrosis requires particular attention. In fact, we demonstrated that CD3+ cells were sig-