Endoscopic application of polysaccharide powder for hemostasis in anticoagulated pigs (with video)

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Background: Acute GI bleeding remains a clinical problem of daily importance. Increasing numbers of patients with compromised coagulation challenge the established methods of endoscopic hemostasis. Therefore, new powders for the treatment of GI bleeding have been developed.

Objective: To clarify the efficacy of a newly available anticoagulant powder in stopping hemorrhage.

Design: A randomized prospective comparative study regarding the potential of an endoscopically applicable polysaccharide powder in pigs receiving antithrombotic medication.

Setting: A professional veterinary animal laboratory.

Patients: Twenty-two pigs were anticoagulated with heparin (n = 8), aspirin (n = 8), or no antithrombotic medication (n = 6), in a randomized order.

Interventions: A bleeding ulcer with continuous bleeding (Forrest I b) was established in the stomach. Endoscopic hemostasis was performed using the powder.

Main Outcome Measurements: Time to hemostasis and the amount of powder used were recorded. Follow-up occurred for 3 days, final hemoglobin measurement, followed by autopsy with control for post-interventional bleeding.

Results: Endoscopic hemostasis was successful in all cases. Post-interventional bleeding was not recorded.

Limitations: Animal study, artificial superficial bleeding source.

Conclusion: Polysaccharide powder is able to stop active bleeding from Forrest I b lesions in pigs receiving antithrombotic therapy.

The frequency of acute GI bleeding is estimated to be between 48 and 160 per 100,000 adults per year.[1] The increasing numbers of patients receiving antithrombotic therapy (ATT) challenge the established methods of endoscopic hemostasis. Despite major advances in endoscopic methods, mortality still remains high. One explanation for this is the growing number of patients with significant comorbidity and current ATT.

Against this background, new powders for the endoscopic treatment of GI bleeding have come onto the market in recent years.[2-4] Most of the available data describe clinical results without reference to the coagulation system. Because the value of these new agents in anticoagulated individuals is still unclear, we conducted a randomized prospective comparative study regarding the potential of an endoscopically applicable polysaccharide powder.

Abbreviation: ATT, antithrombotic therapy.

DISCLOSURE: *The following author received research support for this study from Micro-Tech Europe GmbH: G. Kaehler. All other authors disclosed no financial relationships relevant to this publication.*

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0016-5107

http://dx.doi.org/10.1016/j.gie.2015.02.030

Received August 18, 2014. Accepted February 17, 2015.

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TABLE 1. Comparison of animals with and without antithrombotic therapy

	All (n = 22)	Aspisol (n = 8)	Heparin (n = 8)	Control (n = 6)	*P* value
Median weight, kg (range)	26.2 (19-39)	24.7 (20.4-29)	25.6 (19-35)	28.2 (20-39)	
Median no. of EndoClot applications (range)	2.54 (1-5)	2.75 (2-5)	2.88 (2-4)	2 (1-4)	.245198566
Median amount of EndoClot for hemostasis, g (range)	3.42 (2-8)	(2-8)	3.75 (2-8)	2.5 (2-4)	.161118995
Median time until hemostasis, min (range)	09:41 (2:08-23:00)	10:39 (3:50-20:35)	11:30 (2:45-23:00)	05:15 (2:08-10:20)	.055957075

METHODS

To compare the effectiveness of the polysaccharide powder in pigs with and without ATT, we performed a prospective randomized comparative study in 22 minipigs. The study was approved by the local animal protection committee (Thüringer Landesamt für Lebensmittelsicherheit und Verbraucherschutz no. 08-003/11). Main outcome parameters were hemostasis, the time to achieve hemostasis, and the amount of powder to achieve hemostasis.

Eight pigs were treated with aspisol (250 mg aspirin intravenously; Bayer Health Care AG, Leverkusen, Germany), 8 received heparin (200 international units heparinnatrium/kg body weight; Ratiopharm GmbH, Ulm, Germany), and 6 served as controls. The tests were performed in a randomized order. After establishing general anesthesia with tracheal intubation, a standard EGD with a therapeutic gastroscope (GIF-2TH180 Evis Exera II; Olympus GmbH Medical Systems, Hamburg, Germany) was carried out. The endoscopist (G.K.) was blinded regarding pretreatment with ATT. A 20-mm bleeding ulcer in the major curve of the gastric corpus was then created by a "cold snare" removal of approximately 2 cm^2 using a standard polypectomy snare (30 mm POL1-B1-30-23-220-OL; Medwork GmbH, Höchstadt, Aisch, Germany). This lesion with active bleeding was regarded as a Forrest I b equivalent.

The lesion was treated with 2 g EndoClot (EndoClot Plus Inc, Santa Clara, Calif.). The powder was applied with strict avoidance of any fluid reflux to the catheter system until the bleeding had stopped (Video 1, available online at www.giejournal.org). The ulcer site was observed for a minimum of 2 minutes; if further bleeding occurred, the site was washed with an Endo-Washer (AFU-100; Olympus GmbH Medical Systems) to remove blood and powder remnants. The procedure was repeated until a permanent hemostasis was achieved. Finally, blood and other fluids were removed from the stomach by suction. Hemoglobin was measured before and after the procedure.

After extubation, the pigs were returned to their stable with a fluid intake during the same day and normal food from postoperative day 1. They were observed for behavior and nutrition uptake. On postoperative day 3, their hemoglobin measurement was repeated, after which they were killed. The autopsy followed a protocol with inspection for any bloody content of the peritoneum, stomach, and small and large bowel. The absence of blood throughout the entire intestinal tract indicated they could be classified as having no sign of further GI bleeding.

Statistical analysis was performed using the *t* test. The level of statistical significance was set at $P < .05$.

RESULTS

Endoscopic hemostasis could be achieved with EndoClot alone in all cases with a mean application of 3.42 g polysaccharide powder (range, 2-8; median, 3). The application time was a mean of 9:41 minutes (range, 2:08-23:00; median, 9:55).

In the heparin group the application time was a mean of 11:30 minutes (range, 2:45-23:00; median, 10:55), in the aspisol group 10:39 minutes (range, 3:50-20:35; median, 10:05), and in the control group 5:15 minutes (range, 2:08-10:20; median, 3:32). The amount of powder needed to achieve complete hemostasis was 3.75 g (range, 2-8; mean, 3.5) in the heparin group, 4.0 g (range, 2-8; mean, 3.5) in the aspisol group, and 2.5 g (range, 2-4; mean, 2.0) in the control group (Table 1).

The differences between the ATT groups and the controls were not statistically significant because of the high variance. No post-interventional bleeding was recorded, and hemoglobin measurements showed no decrease.

DISCUSSION

Patients at risk of thromboembolic adverse events place the physician in a therapeutic dilemma. It is known that ATT, especially double medications, elevate the risk of GI bleeding.[5,6] Many patients after cardiologic or cardiosurgical interventions receive a combination of different drugs to prevent hazardous thromboembolic events. Thus, endoscopic treatment of acute GI bleeding is increasingly needed by these patients. Consequently, we see a need for hemostatic methods that work independently from physiologic coagulation.

Organic powders have been found to achieve immediate hemostasis in different fields of surgery. Derived from purified plant starch, EndoClot is a powder with a

molecular structure of modified polysaccharides. Its active principle is rapid water absorption from the blood. The following dehydration process leads to a high concentration of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc) that accelerate the normal physiologic clotting cascade. Polysaccharide powder was found to be effective in the support of wound healing and in thoracic and vascular surgery.[3,4,7] These encouraging results suggest the possibility of endoscopic applicability of these hemostatic powders. Related to the enormous absorption capability of the powder, it is crucial to develop an application technique that avoids a reflux of any fluid to the application system.

Two systems for endoscopic application of such powders are available: Hemospray (Wilson-Cook Medical Inc,Winston-Salem, NC) and EndoClot.[2-4,7] Several case series report the applicability and efficacy of Hemospray for bleeding lesions and for Endo-Clot in the prevention of bleeding after EMR.[3] Except for Holster et al,[2] reporting on 8 patients with ATT and upper GI bleeding treated successfully with Hemospray in 5 of 8 patients, data are lacking about the function of hemostatic powders in anticoagulated individuals. We therefore conducted this comparative study to clarify the potential of EndoClot in the treatment of bleeding GI lesions under conditions of ATT. It is remarkable that hemostatic powders are regarded as technical products from a legal point of view. This may explain how these products came onto the market without comprehensive data about their indications and contraindications, as would be seen in pharmacologic products.

The minipig is generally accepted as a good animal model to simulate GI diseases and their endoscopic management. The application of aspisol for platelet aggregation inhibition and heparin for the reduction of plasmatic coagulation represents both basic types of coagulation disorders. The dosage used was found to be active in previous tests from our team.[8] In that series the same dosage caused spontaneous bleeding, which was not observed in this series.

The experimental model used to create mucosal ulcers by snaring without electrical current mimics superficial lesions and bleeding sources. Therefore, the results of this study cannot be applied for arterial bleeding like Forrest I a. We found that EndoClot was able to stop the simulated Forrest I b lesions in every case. The expenditure, represented by the amount of powder and the time needed to achieve compete hemostasis, did not differ significantly (Table 1). These results are not surprising considering the principle on how these powders act. For users of hemostatic powders in anticoagulated patients, it is important to know they should expect a longer application time and may need to repeat the applications until complete hemostasis occurs.

In conclusion, polysaccharide powder (EndoClot) is able to stop active (nonarterial) bleeding from Forrest I b lesions in pigs receiving ATT. It is a new option for the endoscopic treatment of superficial GI bleeding in ATT patients. To confirm these experimental data, clinical studies are warranted.

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