Efficacy and safety of bovine activated factors IIa/VIIa/IXa/Xa in patients with active gastrointestinal bleeding: a proof of concept study

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Background and study aims: Endoscopic treatment of active gastrointestinal bleeding often remains difficult, and considerable technical expertise is required. Our aim was to assess the efficacy and safety of endoscopic hemostasis with a liquid combination of bovine activated factors IIa/VIIa/IXa/Xa (SeraSeal).

Methods: Patients with active gastrointestinal bleeding were prospectively included. In group A, 5 mL of bovine activated factors IIa/VIIa/IXa/Xa was topically applied via catheters to the bleeding site as initial hemostasis; group B received a similar application but as rescue therapy after failure of conventional endoscopic hemostasis.

Results: In group A, bleeding was stopped by the agent in 15/22 patients (68%) and by conventional endoscopic hemostasis in 5 of the other 7, with coiling and surgery required for definitive hemostasis in 2. In group B, the addition of the agent definitively stopped bleeding in 13/15 patients (87%), with hemostasis in the remaining 2 achieved with fibrin glue. Rebleeding was observed in 1 patient.

Conclusions: Our proof of concept study suggests that the use of bovine activated factors IIa/VIIa/IXa/Xa might be a safe and effective addition to current endoscopic hemostatic strategies, but further studies are necessary.

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Introduction

Although gastrointestinal bleeding is decreasing, it remains an important cause of morbidity and mortality, with mortality rates between 10% and 14% [1]. Current standard hemostatic methods, such as injection, hemoclips, and argon plasma coagulation (APC) for nonvariceal bleeding and band ligation or injection for variceal bleeding [2, 3], are effective hemostatic treatments in 85% to 95% of patients; however, treatment remains difficult, and technical expertise is required [4, 5]. A liquid formulation of bovine activated factors IIa/VIIa/IXa/Xa (SeraSeal/FastAct; Wortham Laboratories, Chattanooga, Tennessee, USA) has been newly approved by the US Food and Drug Administration (FDA) and complies with the relevant European Union legislation (Conformité Européenne [CE] No. 0653) for intraoperative use in humans as a hemostatic agent, particularly in situations of impaired coagulation [6, 7]. When in contact with bleeding tissue in the gastrointestinal tract, the liquid uses the patient's intrinsic clotting system to form clots that cover the site of bleeding. The agent is not absorbed systemically and therefore appears to carry no risk for systemic toxicity. The aim of this study was to assess the efficacy and safety of bovine activated factors IIa/VIIa/IXa/Xa for endoscopic hemostasis in patients with acute gastrointestinal bleeding.

Patients and methods

Patients

This prospective, multicenter, proof of concept study included consecutive patients with active gastrointestinal bleeding at endoscopy seen between November 2011 and July 2013 at four tertiary referral centers. Only patients with active gastrointestinal bleeding were included. All patients gave written informed consent. The study was approved by the ethics committees of the four centers (ethics approval EK 842/2011) and was conducted in accordance with the Helsinki Declaration in its current form.

Methods

Following endoscopic confirmation of bleeding, 2.5 to 5 mL of liquid activated bovine factors IIa/VIIa/IXa/Xa was topically applied to the bleeding site. The endoscopic examinations and treatments were conducted by highly experienced endoscopists (each having performed more than 5000 individual endoscopic procedures). The delivery device consisted of a 5-mL syringe containing bovine activated factors IIa/VIIa/IXa/Xa. This was plugged onto a standard delivery catheter, either an endoscopic retrograde cholangiopancreatography (ERCP) catheter or a dye-spraying catheter (Boston Scientific, Natick, Massachusetts, USA), that was inserted via the working channel of an endoscope. The agent was then delivered in short spray bursts or direct shots (for 1 – 2 seconds) until hemostasis was confirmed. A maximum of 5 mL of the agent was administered to each patient.

Two groups of patients were used for analysis of this proof of concept study: group A, in which the agent was applied as the first hemostatic method in active gastrointestinal bleeding, and group B, in which it was applied as rescue therapy after failure of a first-line conventional endoscopic method. If the activated factors agent then failed to stop the bleeding, conventional endoscopic hemostatic methods were applied at the discretion of the endoscopist.

Standard medical therapy (e.g., proton pump inhibitors, vasoactive drugs) was continued as clinically needed. Endoscopy was performed if rebleeding was suspected. Rebleeding was defined as hematemesis with fresh blood, rectal bleeding with fresh blood, persistence of melena, hemodynamic instability, a drop in the hemoglobin level of more than 2 g/dL within 24 hours, or direct visualization of bleeding at the treated site.

Patients or caregivers were contacted by phone 30 days after the initial endoscopy to record rebleeding or death.

Statistical analysis

All statistical analyses were performed with MedCalc Software, version 12.7.0 (MedCalc, Ostend, Belgium). Continuous variables were reported as mean ± standard deviation (SD) or as median with range intervals, according to their normal or non-normal distribution; categorical variables were reported as number and percentage of patients. Group comparisons of categorical variables were performed with Fisher's exact test. A *P* value of less than 0.05 was considered to denote statistical significance.

Table 1 Use of bovine activated factors IIa/VIIa/IXa/Xa for hemostasis of active gastrointestinal bleeding: main characteristics of the 37 study patients.

Parameter	Value
Age, mean ± SD, y	68.3 ± 11.2
Gender, n (%)	
Female	11 (29.7)
Male	26 (70.3)
Site of gastrointestinal bleeding, n (%)	
Upper	32 (86.4)
Lower	5 (13.6)
Etiology of gastrointestinal bleeding, n (%)	
Ulcer (duodenal/gastric)	14 (37.8)
(No definitive success with activated factors	3 patients)
After intervention	10 (27.0)
Polypectomy	4 (10.8)
(No definitive success with activated factors	2 patients)
Papillotomy	3 (8.1)
(Rebleeding	1 patient)
Dilation	1 (2.7)
Stent insertion	1 (2.7)
Submucosal dissection	1 (2.7)
Tumor	5 (13.5)
Angiodysplasia	2 (6.25)
(No definitive success with activated factors	1 patient)
Mallory – Weiss tear	2 (6.25)
(No definitive success with activated factors	1 patient)
Esophageal varices	1 (2.7)
Boerhaave syndrome	1 (2.7)
(No definitive success with activated factors	1 patient)
Ingestion of sulfuric acid	1 (2.7)
Sigmoid diverticular bleeding	1 (2.7)
(No definitive success with activated factors	1 patient)
Bovine activated factors as initial hemostatic method, n (%)	
Yes (group A)	22 (59.5)
No (group B)	15 (40.5)
Application device, n (%)	
ERCP catheter	27 (73.0)
Dye-spraying catheter	10 (27.0)
Hemoglobin level at endoscopy, mean ± SD, g/dL	8.9 ± 2.1
Type of bleeding, n (%)	
Spurting	8 (21.6)
Oozing	29 (78.4)

SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography.

Results

Patient characteristics

Our study included 37 patients with gastrointestinal bleeding in whom hemostatic treatment with bovine activated factors IIa/VIIa/IXa/Xa was applied between November 2011 and July 2013. The main characteristics of the patients are presented in ▶ **Table 1**. Of the patients who gave informed consent, 10 had no active bleeding at endoscopy and were therefore excluded.

Overall efficacy and safety of activated factors IIa/VIIa/IXa/Xa

Hemostatic treatment with bovine activated factors IIa/VIIa/IXa/Xa stopped bleeding in 28 of 37 cases (76 %), and the efficacy of the agent was similar whether it was used as a first- or a second-line treatment. Bleeding was stopped definitively in 15 of 22 patients in group A (68 %) and in 13 of 15 patients in group B (87 %; $P = 0.70$).

In 2 patients in group A, spurting bleeding was reduced to oozing; however, conventional endoscopic methods were required to stop the bleeding definitively. Conventional endoscopic methods also stopped bleeding in 3 of the 5 remaining patients, and 2 had to undergo coiling and surgery for definitive hemostasis.

In 13 of the 15 patients in group B (87 %), the addition of bovine activated factors IIa/VIIa/IXa/Xa stopped bleeding definitively. In the remaining 2 patients in group B, fibrin glue stopped the bleeding. Among these 15 patients, 5 had received hemoclipping as their initial treatment; 3 had received suprarenin injection; 1 each had received fibrin glue, band ligation, or APC; and 4 had received a combination of treatments. The latter included a patient with Boerhaave syndrome who had received a Danis stent (CareFusion, San Diego, California, USA).

Rebleeding was observed in only 1 of 28 patients (3.6 %) with initially successful hemostatic treatment. The rate of hemostasis was similar whether the agent was applied with an ERCP catheter

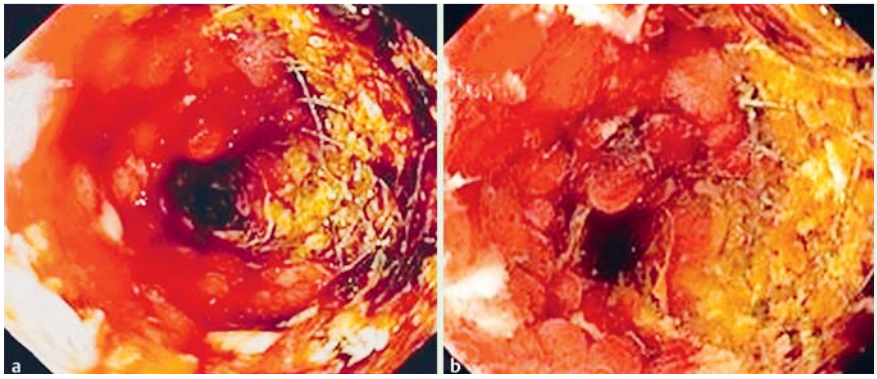

Fig. 1 **a** Bleeding from a tumor through an enteral stent in the duodenum. **b** The bleeding was stopped with the application of bovine activated factors IIa/VIIa/IXa/Xa (SeraSeal).

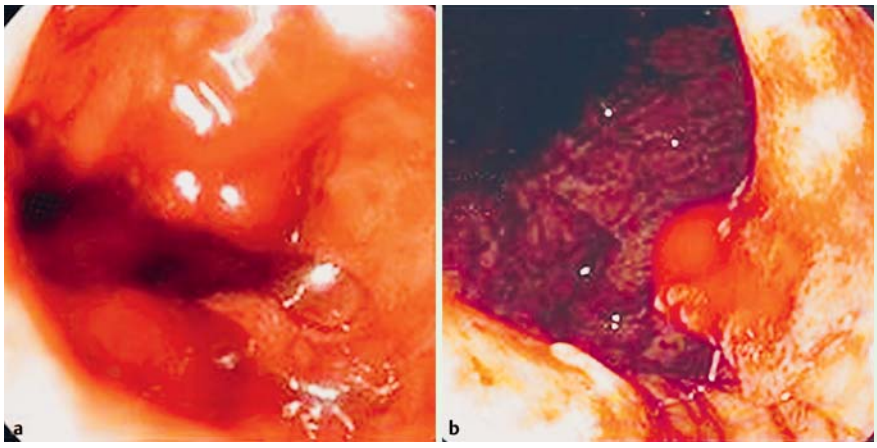

Fig. 2 **a** Bleeding from a Mallory–Weiss tear. **b** The bleeding was reduced with the application of bovine activated factors IIa/VIIa/IXa/Xa. It was finally stopped with a clip.

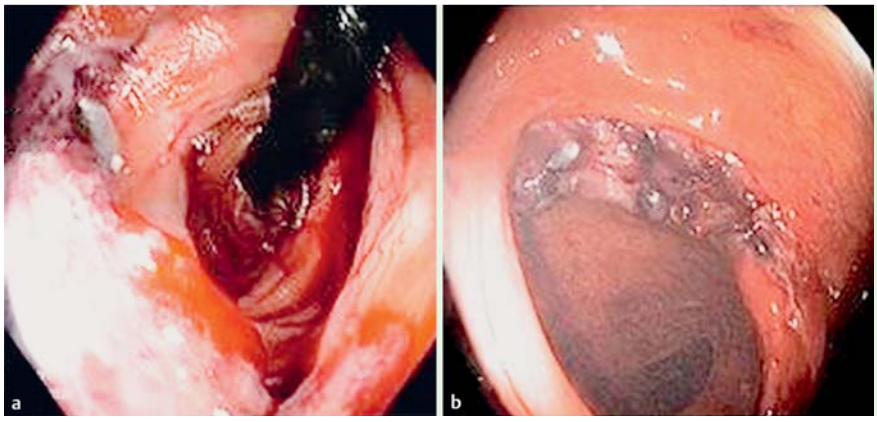

Fig. 3 **a** Bleeding from a large polypectomy site in the cecum. **b** The spurting bleeding was initially reduced with the application of bovine activated factors IIa/VIIa/IXa/Xa. It was finally stopped with a hemostatic clip.

or a dye-spraying catheter: 20 of 27 patients (74%) vs. 8 of 10 patients (80%; $P=0.80$).

Treatment with bovine activated factors IIa/VIIa/IXa/Xa was more effective in patients with oozing (24/29 [83%]) than in patients with spurting bleeding (4/8 [50.0%]), but the difference did not reach statistical significance ($P=0.15$). No bleeding changed from spurting to oozing because of hemodynamic deterioration.

Representative cases of bleeding in which the agent was applied for hemostasis appear in **Fig.1**, **Fig.2**, **Fig.3** and **Video 1**.

No complication related to the application of bovine activated factors IIa/VIIa/IXa/Xa was observed.

The 30-day survival rate was 92% (34/37). The causes of death were tumor progression, liver graft rejection after liver transplant, and decompensation of liver cirrhosis.

Bovine activated factors IIa/VIIa/IXa/Xa for upper gastrointestinal bleeding (32 patients)

The overall success rate of the activated factors agent for patients with upper gastrointestinal bleeding was 84.3% (27/32) and was similar whether it was used as a first-line or a second-line hemostatic method: 82% (14/17) vs. 87% (13/15; $P=0.90$). The rate of rebleeding was 3.7%.

No significant difference was observed depending on the type of catheter used to apply the agent: 83% for ERCP catheter (20/24 cases) vs. 87.5% for dye-spraying catheter (7/8 cases; $P=0.85$).

The success rate for hemostasis with bovine activated factors IIa/VIIa/IXa/Xa was similar whether the upper gastrointestinal bleeding was spurting or oozing: 67% (4/6 patients) vs. 88% (23/26 patients; $P=0.72$).

Bovine activated factors IIa/VIIa/IXa/Xa for lower gastrointestinal bleeding (5 patients)

The agent was used as a first-line hemostatic treatment for all 5 patients with lower gastrointestinal bleeding included in our study, but the treatment was effective in only 1 patient (20 %), who presented with bleeding in a context of rectal carcinoma.

Bovine activated factors IIa/VIIa/IXa/Xa for duodenal/gastric ulcer bleeding

The overall success rate of the activated factors agent in the patients with upper gastrointestinal bleeding from a duodenal/gastric ulcer was good: 79 % (11/14 patients).

The location of the ulcer was the cardia in 1, corpus/antrum in 6 (2 with visible vessels, 2 with a Dieulafoy lesion), and the duodenum in 7 (3 with visible vessels, 1 with a Dieulafoy lesion). In 6 patients with small ulcers (0.5 – 2 cm), the agent was not successful in the 2 who had Dieulafoy ulcers. In 8 patients with large ulcers (2 – 5 cm, 5 with large visible vessels), it was not effective in 1 of those with a large visible vessel.

The efficacy of treatment with bovine activated factors was excellent either as a first-line or a second-line hemostatic method, and was similar in the two groups: first-line, 4/5 patients (80 %) vs. second-line, 7/9 patients (78 %) (P = 0.86). No rebleeding was observed.

The efficacy of this hemostatic method was similar whether the ulcer bleeding was spurting or oozing: 3/4 patients (75 %) vs. (8/10 patients) (80 %) (P = 0.72).

Discussion

Endoscopic hemostasis of active gastrointestinal bleeding can sometimes be difficult or even impossible when standard techniques are used. Based on this consideration, we investigated a combination of bovine activated clotting factors IIa, VIIa, IXa, and Xa (SeraSeal), approved by the FDA and CE-certified, for hemostasis in surgical interventions [8]. Within recent years, several substances have been evaluated for topical application as hemostatic agents via endoscopy: two powders (Hemospray, Cook Medical, Winston-Salem, North Carolina, USA [5]; and Endoclot, EndoClot Plus, Santa Clara, California, USA [6]) as well as Ankaferd BloodStopper (Ankaferd Health Products, Istanbul, Turkey) [7]. This research prompted us to investigate a promising hemostatic agent, bovine activated factors IIa/VIIa/IXa/Xa, for the same indication. Ours is the first analysis of the efficacy and safety of this agent in patients with acute gastrointestinal bleeding.

The overall efficacy of hemostatic treatment with bovine activated factors IIa/VIIa/IXa/Xa was good (76 %); it was very effective for upper gastrointestinal bleeding (84 %) but had a low success rate (20 %) in our small cohort of 5 patients with lower gastrointestinal bleeding.

Our success rate for the control of upper gastrointestinal bleeding was similar to that reported by Smith et al. [9], who used Hemospray. In comparison with the rate published for the nanopowder by Smith et al. [9], our rebleeding rate was much lower: 3.7 % vs. 16.3 %.

Regarding duodenal/gastric ulcer bleeding, our success rate for bovine activated factors IIa/VIIa/IXa/Xa used as first-line therapy (80 %) was comparable with the 76 % primary hemostasis rate in the study by Smith et al. [9] and the 85 % rate in the study by Sung et al. [5], who used Hemospray in a cohort of 20 patients. The rebleeding rate reported by Sung et al. [5] was 10.5 %, and it was 13.3 % in a recent review of the literature by Masci et al. [10], but in our cohort of patients with ulcer bleeding, no rebleeding was observed. However, our study included a lower number of patients with spurting bleeding (corresponding to Forrest class Ia). In 2 patients, spurting bleeding was reduced to oozing. Even if definitive hemostasis cannot be achieved with bovine activated factors IIa/VIIa/IXa/Xa, this agent can reduce the intensity of bleeding, allowing better visibility and higher success rates with subsequent hemostatic methods.

No complication related to the application of bovine activated factors IIa/VIIa/IXa/Xa was observed in our cohort. Our study reflects a cohort of patients who were difficult to treat: 71 % of our patients were older than 60 years, 29 % were older than 75 years, and all had co-morbidities. In the patient with Boerhaave syndrome, a Danis stent and bovine activated factors treatment, followed by fibrin glue, were chosen because he was considered too sick to undergo surgery. He had a stable course afterward. The causes of death within 30 days after endoscopy were all related to co-morbidities, not to failure of hemostasis or to rebleeding. Interestingly, SeraSeal was even more effective as second-line therapy, indicating its possible value as rescue therapy.

The decision on whether to use a dye-spraying catheter, which might be beneficial for diffuse circular bleeding, or an ERCP catheter, which is quite similar to those used with the Hemospray device and allows punctate application, was left to the discretion of the individual endoscopists.

We also attempted to analyze the efficacy of SeraSeal for patients with acute lower gastrointestinal bleeding, but only 5 patients were included in the study, so we could not draw scientifically valid conclusions. In this small cohort, the novel hemostatic agent controlled bleeding in only 1 patient, who presented with bleeding in the context of rectal carcinoma.

Another limitation of the study is that not all consecutive patients with active gastrointestinal bleeding were included, for several reasons: there is no established method for the central reporting of emergency endoscopic procedures within the trial centers; only the involved and highly trained endoscopists were allowed to include patients; some patients were not capable of

Video 1

Effects of the application of bovine activated factors IIa/VIIa/IXa/Xa (SeraSeal) to treat gastrointestinal bleeding at various sites. Online content including video sequences viewable at: http://dx.doi.org/10.1055/s-0034-1393312

giving informed consent because of their severe disease; and some patients did not have active bleeding at endoscopy.

Because it is a liquid, SeraSeal should be investigated in future trials in patients who have bleeding within a small lumen, such as the bile duct, or pulmonary bleeding. Further studies with comparative groups are needed to determine the true merit of this topical agent.

In conclusion, our proof of concept study suggests that an agent comprising bovine activated factors IIa/VIIa/IXa/Xa (SeraSeal) might be a safe and effective addition to current endoscopic hemostatic strategies, but further studies are necessary.

Competing interests: None

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