



The Effect of Hemostasis Powder® on Treatment of Bleeding from Benign Ulcers of Upper Gastrointestinal Tract; A Pilot Study

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ABSTRACT

BACKGROUND

Gastrointestinal (GI) bleeding is one of the most prevalent internal medical emergencies. Despite using several methods of treatment, effective treatment cannot be achieved in some patients. Hemostasis powder® is a mineral-herbal product. This emulsion was able to coagulate blood in, in vitro studies and also was effective in the treatment of mucosal and cutaneous bleeding in animal studies, without any toxicity. We decided to compare its effect on the treatment of human GI bleeding with the other common method for treatment of GI bleeding “argon plasma coagulation plus epinephrine injection” in a pilot randomized clinical trial.

METHODS

The patients with GI bleeding who were admitted to the emergency wards of Ghaem and Imam-Reza Hospitals in Mashhad were randomized to treatment with Hemostasis powder® or “argon plasma coagulation plus epinephrine injection” method, with randomized doctors, after complete testimonial sheet. The patients underwent re-endoscopy to evaluate the ulcers 3 days later, and were under observation for 3 months. After achieving the number of patients that was planned (20 patients), all data were entered to SPSS software version 20 and were analyzed with parametric and non-parametric tests.

RESULTS

The treatment success was 95% in both groups. There was no complication after treatment of GI bleeding in the two groups after 3 months. No rebleeding was reported in Hemostasis powder® group but 10 % was reported in “argon plasma coagulation plus epinephrine injection” group.

CONCLUSION

It seems that if the successful results occur in the future complimentary studies, Hemostasis powder® can be used as a new, effective, available, and inexpensive measure in the treatment of GI bleeding and also in the GI bleedings that cannot be treated with common available methods.

KEYWORDS:

Gastrointestinal bleeding, Samen-ista emulsion, Argon plasma coagulation, Hemostasis powder®

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INTRODUCTION

Gastrointestinal (GI) bleeding is still one of the most important emergency cases in GI diseases. Despite the decrease in mortality, its incidence is still high, in 5-10% of patients with peptic ulcer, and in about 15% of people with esophageal varices.¹ It is estimated that the annual rate of hospital admissions due to acute upper GI bleeding in the United States is 160 per 100000 populations,

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exceeding 400000 per year.² The mortality rate has remained between 7% and 10% over the past 30 years.³ In the United States, direct medical costs are estimated at \$2 billion a year to care for patients who have gastric ulcer bleeding.⁴ In most patients, most of acute cases of upper GI bleeding (80% to 90%) have causes other than variceal, and gastric ulcers are the cause of most of these lesions.⁵ Recent population-based estimates have shown that the incidence of GI bleeding is about 60 per 100,000 populations,⁶ and it is higher in people with a history of consuming aspirin and non-steroidal anti-inflammatory drugs. In addition, gastric ulcer bleeding is seen mainly among the elderly, with 68% of the patients over the age of 60 years and 27% over 80 years.⁷ The first line treatment for acute upper GI bleeding, especially gastric ulcer hemorrhage, is endoscopic hemostasis. Typical methods include epinephrine injection, thermal coagulation using a heater probe or monopolar probe, and mechanical hemostasis using hemoclips. Combination therapy of endoscopy and injection, thermal, and mechanical methods is very effective and primary hemostasis is obtained in 85% to 95% of cases.⁸⁻⁹ however, about 5% to 10% of patients still have bleeding after primary hemostasis with combined endoscopic therapy.¹⁰ Endoscopic treatment for upper GI bleeding is not always easy and can be challenging in some cases, as bleeding may be arisen from places that can be difficult to access, such as the duodenal posterior wall or proximal lesser curvature of the stomach. This can create problems for the placement of hemoclips or appropriate pressure with coagulation probes for treatment action. In some cases, the lesions can be large with active bleeding, which makes it difficult to locate the lesion and conduct treatment. In such cases, a high level of technical expertise is often required to control bleeding while is not always available. Due to these problems, it is necessary to investigate the development of alternative methods of endoscopic hemostasis to control GI bleeding in these cases. One of the new treatment methods for controlling GI bleeding is the use of hemostatic powders that are sprayed by the endoscope to the ulcer. By using the powder, a barrier is usually created on the wall of the vein when the powder is contacted with the bleeding site, resulting in the rapid bleeding stop. So far, some limited types of these powders have been produced, most notably Hemospray or

TC-325, which is a powder containing human or animal proteins that is neither absorbed nor metabolized in the human body. For this reason, it is known as a non-toxic substance. The exact mechanism of action is unknown, but the powder in contact with water creates a sticky material that covers the tissue and creates a mechanical tamponade. After 24-72 hours, this coating falls into the lumen and is generally eliminated from the GI tract.¹¹

Endoclot PHS is the other powder composed of a starch-derived material, which is a non-absorbable and hemostatic polysaccharide. After binding to the blood, it quickly absorbs water and increases the concentration of platelets, red blood cells, and coagulation proteins at the site of bleeding. In total, a gel powder is produced that adheres to the site of the ulcer. This gel is detached from the scar in a few hours or days.¹¹ The third powder is called ABS, a mixture of plants. In the laboratory phase, it has been shown that this substance creates a protein network that is a place for aggregation of red cells, activated white blood cells, and coagulation proteins.¹¹

In this study, we investigated the effect of another powder called Hemostasis powder® on GI bleeding control. Hemostasis powder® (the previous name for this powder was Samen-ista) is a new drug that is effective in controlling GI bleeding by activating the coagulation cascade.

MATERIALS AND METHODS

Our study was a prospective clinical trial that was designed as a pilot study. This study lasted from (March 2016) to (March 2017), and conducted on patients with upper GI bleeding referring to the Emergency Department of Ghaem and Imam Reza Hospitals in Mashhad. During the initial endoscopy, the origin of bleeding from upper GI tract was diagnosed in the patients. In this study, the exclusion criteria were hemorrhages due to esophageal or gastric varices or hemorrhage due to esophageal or gastric malignancies and kidney failure, as well as bleeding in patients with coagulation disorders or those using anticoagulant drugs such as warfarin. In total, 40 patients with upper GI bleeding were included in the study according to the inclusion criteria. The patients were randomly divided into two groups of control and case. Hemorrhage was treated with argon plasma method (combination of injection of diluted epinephrine and

Argon plasma coagulation (APC)) in the control group and with Hemostasis powder® in the case group.

The patients included in the study were monitored for a period of 3 months in both case and control groups. At the end of the 3 months, the patients were contacted to record the incidence of any complications or re-bleeding (diagnosed by gastroenterologist based on history) in the patients' questionnaire. After reaching the target sample size (20 patients), the data of the two groups were compared using statistical methods. Statistical analysis was done using SPSS software version 20. Frequency table and descriptive statistics were used to describe the data. Chi-square and non-parametric Kruskal-Wallis tests were used to compare the two groups.

The study protocol was designed based on the Helsinki Declaration on Ethics and was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, Iran (IR.MUMS.REC.1394.564). This study was also designed based on ethical and religious norms related to the community and the confidentiality of data is fully respected by the authors of the study. This drug and its possible side effects were clearly explained to the patients by a physician.

Written informed consent was obtained from all patients. People entering the study could withdraw from the study at any time without affecting their treatment process. All tests and medications were free of charge. This study was registered in the Iranian Registry of Clinical Trials (IRCT2016033118915N4).

Introducing Hemostasis powder®

Hemostasis powder® is a new plant emulsion that has been developed through the cooperation between the Departments of Pharmacology, and Digestion, and medical faculty of Mashhad University of Medical Sciences. The drug was approved by the Iranian Food and Drug Administration and the Ministry of Health and Medical Education. This drug was made in a powder form in two vials, called Tabashir and Mazo powders, which turns into emulsion using a solvent placed next to the vials when using. Before this study, the effect of the drug on bleeding control and its safety was investigated in an animal study.¹²

Procedure of Hemostasis powder® application: In the case group, Hemostasis powder® drug prepared as

powder and solvent was used for treatment. Before using, the powder was mixed with the solvent to prepare Hemostasis powder®. Using a catheter (10 Fr) inserted into the endoscope (Olympus, Japan), first Tabashir solution and then Mazo solution was poured on the bleeding ulcer from a 1 to 2 mm distance. The bleeding site was observed for 1 minute in the endoscope, and if the bleeding stopped completely, the endoscopic treatment was terminated. However, if any sign of bleeding remained even in a low extent, this was considered as a failure and depending on the case, common treatments as the same as for other patients were applied to treat bleeding. The failure of Hemostasis powder® was defined as the inability to achieve acute homeostasis after using 20 gr Hemostasis powder®.

RESULTS

In total, 26 men (65%) and 14 women (35%) were randomly assigned to the study. In the Hemostasis powder® group, 14 men and 6 women and in the argon plasma coagulation plus epinephrine injection group, 11 men and 9 women were recruited randomly. The mean age of the study population was 61.9 years. It was 65 years in the Hemostasis powder® group and 59 in the argon plasma coagulation plus epinephrine injection group. The age of the subjects did not differ significantly between the two groups. In the Hemostasis powder® group, the types of GI ulcers that were treated in the study were 15 of ulcer, 3 of pigmented haematin on ulcer base, 1 of visible vein, and 1 of adherent clot. The most common ulcer sites in this group were the stomach in 12 cases, the duodenum in 6 cases, and the esophagus in 2 cases. In the argon-plasma group, there were 15 cases of ulcer and 5 cases of visible vein. The ulcer sites were equally distributed in this group: 10 cases in the duodenum and 10 cases in the stomach. Patients' profile is shown in table 1.

Regarding the inclusion criteria, none of the patients with ulcer had endoscopic malignancy and none of them had severe background diseases. In total, the success of the treatment was 95% in both methods. There was no significant difference between the methods in the control of bleeding. In the 3-month follow-up, no specific complication was observed in patients treated with Hemostasis powder®. The rate of recurrent hemorrhage in the control group was 10% (two cases) and in the patients

Table 1: Profile of participants in the study

Variable	(N:20) Hemostasis powder®	argon plasma coagulation plus epinephrine injection (N:20)	P value
Age (years)	65	59	0.6
Sex (male)	14	11	0.56
Endoscopy lesion	Ulcer with oozing (FC I) : 15 pigmented haematin on ulcer base (FC II): 3 visible vessel (FC II): 1 adherent clot (FC II):1	Ulcer with oozing (FC I) : 15 visible vessel (FC II) : 5	
Location of lesion	Stomach :12 Duodenum : 6 Esophagus : 2	Stomach :10 Duodenum : 10	
Treatment response	95 %	95%	
Rebleeding (3-month period)	0	2 (10%)	0.04

FC I: Forest classification I
FC II: Forest classification II

treated with Hemostasis powder® was zero percent. Both patients with recurrent hemorrhage in the control group (argon plasma coagulation plus epinephrine injection) had gastric ulcer with visible vein, and aged 55 and 61 years.

DISCUSSION

Hemostatic powders are alternative treatment for controlling GI bleeding. They work in two different ways: first, they prevent hemorrhage as a mechanical barrier and second, they induce anticoagulant effects by systemic absorption. When the drug is contacted with the location of the bleeding, the powder forms an obstacle on the vascular wall, rapidly stopping the bleeding. In the next stage, the absorption of the powder increases the concentration of coagulation factors and increases the formation of clot. Previous versions of these drugs have had a good effect on immediate bleeding control.

In this study, we investigated the effect of Hemostasis powder® on controlling upper GI bleeding compared with the effect of treatment with argon plasma coagulation plus epinephrine injection method.

Overall, the success rate of treatment in both methods was 95% and there was no significant difference in the use of the two methods. However, as previously mentioned, in this study, bleeding due to varices, malignant ulcers or GI lesions, and ulcers with spurting bleeding were not included in the study. This was because this study was carried out as a pilot study for the first time on human

subjects and it was advisable to treat low-risk ulcers in the first stage using this new method and then, to use the solution of Hemostasis powder® to treat high-risk ulcers in a subsequent study.

It should be noted that before the start of this pilot study, the effect of Hemostasis powder® in the laboratory and then animal studies was evaluated.¹² In the animal study, the effect of the solution on the control of bleeding due to cutting off the rabbit's ear was compared in the two groups of cases and controls.¹² The results showed that Hemostasis powder® could significantly reduce the bleeding time. Next, the effect of the solution on the control of bleeding caused by cutting off the distal part of the tail of the mice was investigated.¹² In this case, the bleeding stopped significantly more quickly. Finally, the effect of pouring the solution on the gastric ulcer of rabbit during endoscopy was investigated. In this stage, bleeding stopped significantly and more quickly again.¹²

In similar studies in other parts of the world, the effects of hemostatic powders on GI bleeding have been studied. For example, TC-325 or Hemospray (Hemospray; Cook Medicine, Winston-Salem, North Carolina, USA) is a new powder approved for endoscopic treatment. This powder has been used for many years in the battlefield to control bleeding, especially in arterial ulcers. The powder was used in a clinical study by Sung and colleagues on 20 patients with gastric ulcers with active bleeding. The results showed that the drug could control bleeding in 95% of the patients. The only patient who failed had

bleeding from pseudoaneurysm. After 3 days, Hemospray was removed from the stomach and duodenum in all patients and no adverse effects were observed.¹³

In another study, complications such as visceral artery aneurysms and acute splenic infarction have been reported for Hemospray.¹⁴ In another report, this powder was used for salvage treatment in 108 patients, most of whom had gastric ulcers or gastric tumors. The bleeding was immediately controlled in 96.5% of the subjects.¹⁵ The success rate of the Hemostasis powder® is quite comparable to these agents. A remarkable point in the study of Hadara and co-workers on the use of TC-325 was the recurrence of bleeding that occurred in 26.7% of the cases on day 8 and in 33.5% on day 30 after treatment.¹⁵ In another study, the rate of recurrent bleeding was 38.9% in the first 7 days after treatment.¹⁴ The rate of recurrent bleeding in a large study in our country in patients with peptic ulcer treated with classic endoscopic treatments was 16.5%.¹⁶ Compared to these studies, the strength of Hemostasis powder® was its ability to reduce recurrent bleeding because in the course of our 3-month period, we did not see any recurrence of bleeding in those treated with this drug. Of course, this success could be attributed to the population of the study. However, this could be a significant point in larger studies on this drug.

In addition to immediate bleeding control, hemostatic powders have other benefits, one of which is the ease of use of the drug without the need for advanced technical skills in emergencies where any endoscopist is not available. Another important advantage of these medications is that precise targeting is not required for drug injection, and it is easy to use in cases in which the site of the wound is difficult to access.¹⁷ Another benefit is the lack of need for injecting needle that reduces the risk of damage to other tissues (due to needle-stick contact with the mucosa), which can worsen bleeding and even lead to mucous perforation, if occurs.¹⁸

In addition, these drugs, due to their ability to cover vast areas with multiple bleeding points, are appropriate choices for treating bleeding from hemorrhagic gastritis, gastric artery ectasia, mucosal damage caused by radiotherapy, and hemorrhage associated with malignancy.¹⁸ In this study, a 3-month follow-up survey did not show any specific complication due to drug use. In an animal study, all mice and rabbits treated with Hemostasis

powder® solution were killed and all of their end organs as well as the stomach were sent for pathological examination to determine the probability of toxicity of the solution, which showed no pathological lesions in these organs.¹²

In general, considering the acceptable success rate of treatment for benign hemorrhages of the upper GI tract using Hemostasis powder® solution, as well as due to no poisoning effect or any other complications after the use, it seems that we can conduct the next phases of the study especially on larger sample sizes and other GI ulcers, to pave the way for more comprehensive use of this solution in the treatment of GI ulcers. The use of these alternative methods can greatly help control GI bleeding caused by ulcers, especially in cases where classical treatments cannot be used due to the size or location of the ulcers.

CONCLUSION

Hemostasis powder®, as an effective and easy-to-use treatment, can be considered as a promising method for treating GI bleeding.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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