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EDITORIAL

Ankaferd hemostat in the management of gastrointestinal hemorrhages

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Abstract

Gastrointestinal (GI) bleeding refers to any hemorrhage ascribed to the pathologies of the gastrointestinal tract, extending from the mouth to the anal canal. Despite the recent improvements in the endoscopic, hemostatic and adjuvant pharmacologic techniques, the reported mortality is still around 5%-10% for peptic ulcer bleeding and about 15%-20% for variceal hemorrhages. Although endoscopic management reduces the rates of re-bleeding, surgery, and mortality in active bleeding; early recurrence ratios still occur in around 20% of the cases even with effective initial hemostatic measures. In this quest for an alternative pro-hemostatic agent for the management of GI bleedings, Ankaferd blood stopper (ABS) offers a successful candidate, specifically for "difficult-to-manage" situations as evidenced by data presented in several studies. ABS is a standardized mixture of the plants Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica. It is effective in both bleeding individuals with normal hemostatic parameters and in patients with deficient primary and/or secondary hemostasis. ABS also modulates the cellular apoptotic responses to hemorrhagic stress, as well as hemostatic hemodynamic activity. Through its effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and wound healing, ABS is now becoming an effective alternative hemostatic medicine for gastrointestinal bleedings that are resistant to conventional anti-hemorrhagic measurements. The aim of this review is to outline current literature experience suggesting the place of ABS in the management of GI bleeding, and potential future controlled trials in this complicated field.

Key words: Ankaferd blood stopper; Gastrointestinal bleeding; Hemostasis; Erythrocyte aggregation; Coagulation

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INTRODUCTION AND BACKGROUND OF ANKAFERD BLOOD STOPPER

Ankaferd is a traditional herbal medicine that has been used in Anatolia as a hemostatic agent for centuries[1]. Ankaferd is a standardized mixture of the plants *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*, each of which have some effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and/or cell mediators[1-4]. Ankaferd blood stopper (ABS), a novel topical hemostatic agent, has been approved in Turkey for clinical hemorrhages, when the conventional control of bleeding by ligature and/or conventional hemostatic measures is ineffective[5,6]. ABS is clinically effective in bleeding individuals with normal hemostatic parameters and in patients with deficient primary hemostasis and/or secondary hemostasis[7-10]. ABS modulates the cellular apoptotic responses to hemorrhagic stress as well as its hemostatic hemodynamic activity[11], and has many effects on proteins of the tissue and blood. Dose-dependent reversible PAR-1 down-regulation is mediated by ABS and also induces sustained PAR-1 down-regulation in the presence of lipopolysaccharides (LPS). These findings are compatible with other investigations focusing on the endothelial hemostatic molecules, endothelial cell protein C receptor (EPCR) and PAI-1. ABS may act as a topical biological response modifier as along with its anti-hemorrhagic effects[10].

Gastrointestinal (GI) bleeding is a potentially life-threatening condition and a common cause of hospitalization. Despite effective endoscopic treatments, it is responsible for a significant societal burden due to the associated morbidity, mortality and financial implications[12]. Although endoscopic management does diminish the rates of rebleeding, surgery, and mortality in active hemorrhage, early recurrence still occurs in around 20% of cases despite the effective initial hemostasis. Hence, there is an ongoing intensive search for novel techniques or treatments that are effective, safe and "potentially life-saving" in the distinct settings of GI bleedings. During the search for a complementary pro-hemostatic agent for the management of GI hemorrhages, accumulated evidence suggested that ABS could have an efficient place for the "difficult-to-manage" subtypes of GI bleedings[13-22]. ABS may serve as an adjuvant and/or primary agent for this complicated area.

The aim of this review is to outline the current literature suggesting the place of ABS in the management of GI bleeding, and potential future controlled trials in this complicated field. Currently established standard medical and endoscopic therapeutic options with hemostatic approaches do not represent the primary scope of this paper.

ABS AS A MODERN TOPICAL HEMOSTATIC AGENT

The basic mechanism of action for ABS appears to be the formation of an encapsulated protein network that provides focal points for erythrocyte aggregation. Rather than affecting an individual clotting factor, this protein mesh affects the entire physiological hemostatic process that controls bleeding[1,2]. Blood cells, particularly erythrocytes and activated leukocytes, were found to aggregate rapidly in the presence of ABS, thereby participating in the network formation (Figure 1). Macroscopic hemostatic actions of ABS may be explained by its rapid (< 1 s) induction of a protein network in human plasma and serum samples[23]. ABS-induced formation of the protein network with vital erythroid aggregation covers the entire physiological hemostatic process[1,2]. There are distinct important components of the ABS-induced hemostatic network. Vital erythroid aggregation takes place with the spectrin and ankyrin receptors on the surface of red blood cells. Those proteins, and the required ATP bioenergy, are included in the ABS protein library. Ankaferd also upregulates the GATA/FOG transcription system affecting erythroid functions. Urotensin-Ⅱ is also an essential component of Ankaferd and represents the link between injured vascular endothe-

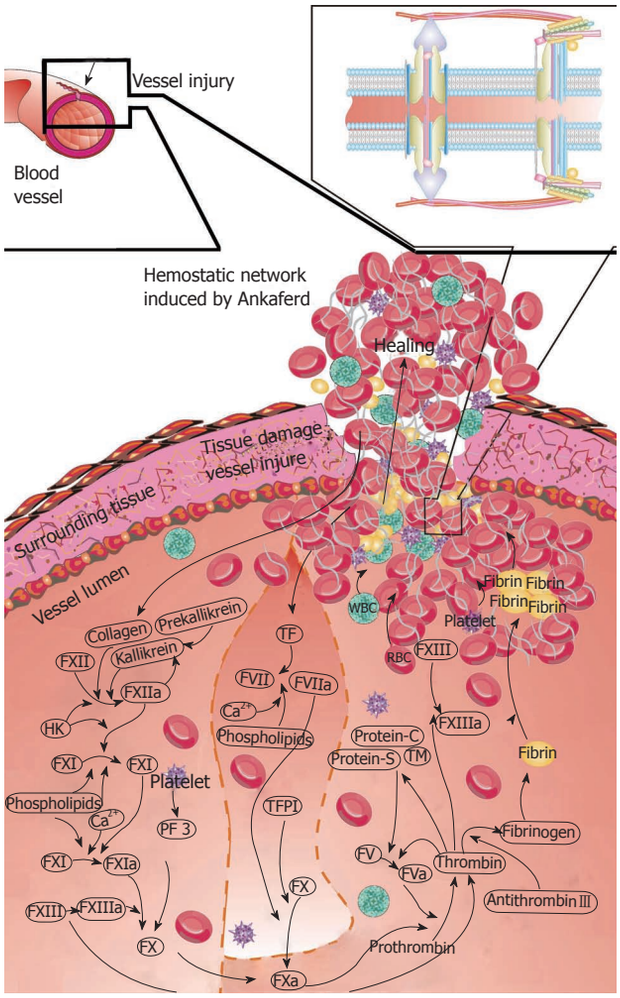

Figure 1 The basic mechanism of action for ankaferd blood stopper is the formation of an encapsulated protein network that provides focal points for erythrocyte aggregation. Ankaferd blood stopper (ABS)-induced formation of the unique protein network within the vital erythroid aggregation covers the entire physiological haemostatic process. Red blood cell (RBC) elements (such as spectrin and ankrin surface receptors, and internal ferrochelatase enzyme), related transcription factors (such as GATA-1) and RBC-related proteins (such as urotensin Ⅱ) are the main targets of ABS. Those proteins and the required adenosine triphosphate bioenergy are included in the protein library of Ankaferd[1].

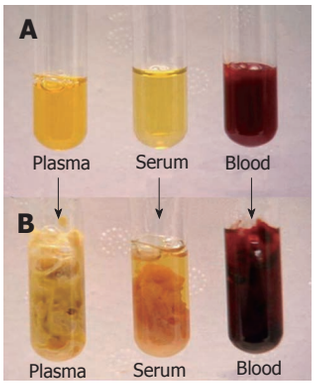

Figure 2 Ankaferd blood stopper-induced protein network formation within less than 1 s. Plasma under the light microscopy before (A) and just after (B) Ankaferd application[1].

lium, adhesive proteins, and active erythroid cells[1,2]. These concepts have been developed *via* matrix-assisted laser desorption/ionization time of flight proteomic molecular analyses, cytometric arrays, transcription analysis, and Scanning electron microscopy ultrastructural examinations, as well as numerous investigations interacting with *in vivo* research settings[23-26].

In vitro tests demonstrated that coagulation proteins were not individually affected by the addition of ABS to fresh normal plasma or serum, whereas plasma fibrinogen activity decreased from 302 to < 10 mg/dL, and fibrinogen antigen decreased from 299 mg/dL to < 30 mg/dL in parallel with thrombin time prolongation. Total protein, albumin and globulin levels decreased after the addition of ABS to fresh serum[2,23]. These studies suggested that the ABS-induced network formation depends upon interactions between ABS and blood proteins, such as fibrinogen, and that ABS might affect fibrinogen and other proteins *via* agglutination of these molecules. Figure 2 depicts the macroscopic appearance of the protein network formation before and after adding ABS to human plasma, serum and whole blood.

Dose-dependent reversible PAR-1 down-regulation is mediated by ABS inside the human umbilical vein endothelial cells. ABS induces sustained PAR-1 down-regulation in the presence of LPS. These findings are compatible with our previous investigation focusing on the endothelial hemostatic molecules, EPCR and PAI-1. ABS has dual diverse dynamic reversible actions on EPCR and PAI-1 inside vascular endothelial cells also in the model of human umbilical vein endothelial cells. Sudden anti-hemorrhagic efficacy of ABS *via* immediate enhanced expression of pro-hemostatic PAI-1 and down-regulated anti-coagulant EPCR upon the exposure of ABS have been recognized as the unique hemostatic effects of ABS. The hemostatic function of PAR-1 is mainly prothrombotic. Significant PAR-1 down-regulation mediated by ABS indicated that ABS has balanced effects on global hemostasis[2,26,27]. Coagulation proteins, namely factor Ⅱ, Ⅴ, Ⅶ, Ⅷ, Ⅸ, Ⅹ, Ⅺ and Ⅻ, were not affected *in vitro* individually by ABS[17]. Likewise, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal *via* the application of ABS. However, prolonged thrombin time (TT) was evident[2]. Since PAR-1 is the most important thrombin receptor, depression of PAR-1 with ABS could explain the prolonged TT due to ABS[10,27].

UPPER GASTROINTESTINAL BLEEDING

Peptic ulcer disease

Peptic ulcer is the most common cause of acute hemorrhage in the upper gastrointestinal tract, accounting for 28%-59% of all episodes of upper GI bleeding[28,29]. Endoscopy with hemostatic therapy has clearly been shown to aid in proper diagnosis, prognosticate requirement for blood transfusions and, in the majority of instances, obviates the need for surgical intervention[30,31]. Despite the improvements in achieving hemostasis, recurrent bleeding still occurs in about 15% to 20% of GI bleeding cases. Moreover, the reported mortality for patients with a bleeding peptic ulcer still amounts to 15%[32]. Early effective hemostatic intervention is of great importance in the treatment of bleeding peptic ulcer disease, due to the high risk of morbidity and mortality. However, additional development is eagerly awaited for the therapeutic armamentarium of GI bleeding, which is safe, effective and easy applicable in difficult or intolerant patients[33,34]. In this setting, ABS could be the candidate hemostatic agent in the controlling of peptic ulcer bleeding, based on the previous successful anecdotal reports in GI bleeding with various clinical outcomes[13-22].

There is growing evidence in favor for the use of ABS in distinct states of GI bleeding, particularly in patients with bleeding due to peptic ulcer disease. In an observational study of "intention-to-treat" analysis by Ozaslan *et al*[35], five adult patients with bleeding peptic ulcer disease, in which ABS was used as a primary hemostatic agent due to difficulties or inappropriateness of the conventional measures, were reported to attained success in controlling of the bleeding within minutes. Similarly, Purnak *et al*[36] reported a successful hemostasis control in a patient with a bleeding peptic ulcer complicated with defective hemostasis. In this reported case, at the time of bleeding, the patient was under-treated with a cytotoxic chemotherapeutic agent leading to thrombocytopenia. Furthermore, platelet dysfunction and prolonged PT due to neutropenic sepsis had further complicated the hemostatic status. This "difficult-to-manage" situation was effectively controlled with topical ABS application and provided a critical time gain to the clinician until hemostasis could be returned to the normal level. Since ABS performs cellular hemostasis mainly through erythrocytes, it is reasonable to suggest that bleeding due to defective hemostasis (such as from a low platelet count, due to a warfarin overdose or because of chronic nonsteroidal anti-inflammatory drug use) could be controlled more efficiently with ABS as in this reported case[36]. Likewise, the *in vivo* hemostatic effect of ABS with defective hemostasis, due to aspirin and low-molecular weight heparin administration, has been investigated in experimental models and ABS was found to be effective in shortening the bleeding duration and decreasing the amount of bleeding[37]. Fur-

thermore, the first pediatric experience with ABS in an infant with bleeding peptic ulcer was recently demonstrated by Yarali *et al*[38]. Both of these reports seem to be encouraging for the justification of the use of ABS in peptic ulcer bleeding based on future controlled clinical trials.

Neoplastic upper GI bleedings

GI bleedings due to tumoral lesions (primary gastrointestinal tumors, direct local invasion by other malignancies, or metastatic disease to the gastrointestinal tract) are among the frequently encountered causes of GI bleeding, accounting for nearly 5% of severe upper GI bleeding cases[39]. Severe bleeding is a bad prognostic sign for upper GI tumors, and endoscopic hemostasis in this setting is often a temporary measure prior to staging and surgical resection. Several methods have been used to control bleeding from gastroduodenal malignant lesions, including thermal contact probes (tumor probe, bipolar probes, or heater probe), epinephrine injection, laser coagulation and injection of sodium tetradecyl sulphate with a success rate of 66%-100%[39-41]. Unfortunately, these intervention modalities were associated with high re-bleeding rates; up to 80% in a 1 mo period[39,40].

In the setting of malignant GI bleeding, ABS was effectively used previously in several reports. Application of ABS successfully controlled GI bleeding within seconds in a patient with major GI bleeding from a recurrent lesion at the hepaticojejunostomy anastomosis following surgery for distal cholangiocellular carcinoma[42]. In a case series by Kurt *et al*[43], topical application of ABS in seven patients with neoplastic upper GI hemorrhages, with appropriate bleeding control and post-procedural complications, were documented. In their summary, complete hemostasis was achieved in all of those patients within seconds of the endoscopic topical application of ABS, with no immediate complications. A recent report by Ozaslan *et al*[44] also supported the effectiveness of ABS in tumoral GI bleedings as a primary hemostatic agent. In their observational study, six patients suffering from malignant GI bleeding were reported to achieve hemostasis with topically applied ABS during endoscopy by a sclerotherapy needle or a heater probe catheter. The control of bleeding was obtained with ABS in five cases during the first endoscopic session, while the remaining one required a second application.

Apart from the mechanical hemostasis achieved by ABS, Turhan *et al*[45] disclosed that ABS decreases tumor vascularization in bleeding gastrointestinal carcinomas. In this report, topical ABS was applied in two patients with distinct tumoral GI bleedings due to gastric and rectal cancer. Tumor neo-vascularization/angiogenesis before and after the application of ABS were measured as tumor microvessel density (MVD). Topical ABS administration to the tumoral lesion resulted in complete control of the bleeding. Furthermore, ABS significantly decreased MVD measurements in both of the GI neoplastic tissues in comparison to the MVDs from the biopsy specimens before the ABS administration and the unexposed native neoplastic tissues of the stomach and rectum[45]. Based on these preliminary findings, the authors suggested the presence of a secondary, more sustained, mechanism of hemostasis induced by ABS beyond the initial protein network.

Although the management of tumoral GI bleeding in a pediatric population is a difficult to manage situation, ABS was also shown to be effective in a 10-year-old boy with esophageal tumor bleeding related to disseminated intravascular coagulation (DIC) during the post-chemotherapy period[46]. Since the endoscopic procedure was contraindicated due to DIC and associated co-morbidities in this patient, nasogastric tubes were used for the topical application of ABS. The bleeding was stopped within a very short period of time following the 6 milliliters of topical ABS application, with no observation of re-bleeding or side effects.

Sphincterotomy bleeding

Endoscopic sphincterotomy (EST), which has became an essential procedure in therapeutic endoscopy for the management of pancreatic and biliary problems, raises concerns about procedure-related complications, such as hemorrhages, pancreatitis, cholangitis and perforation[47]. Hemorrhage is one of the most frequently encountered, and sometimes fatal, complications of EST and the incidence is reported as 1%-10%[47]. Though delayed hemorrhage may develop several days after EST, most of the bleedings occur just after EST. For this reason, effective control of intra-procedural hemorrhage is of great importance for the prevention of late post-EST bleedings. Several methods were suggested to control EST-related bleedings, with various grades of success[48]. The classical therapeutic methods for the EST-induced hemorrhages are endoscopic, surgical and radiological interventions. The reported means of endoscopic management consist of: argon plasma coagulation, electrocoagulation, injection therapy with various agents, and hemoclipping[49,50]. Since complete control of hemorrhages are not always possible *via* using those methods, novel hemostatic agents like ABS offer promising results in controlling post-sphincterotomy bleedings. We have recently reported the successful application of ABS in a 43-year-old woman that has underwent ERCP for cholangitis due to multiple bile duct stones[13]. After mild sphincterotomy, early bleeding from the sphincterotomy site was observed. Despite management with electrocoagulation and injection therapy with epinephrine, the bleeding remained uncontrolled. Subsequently, we injected 3 mL of ABS *via* the working channel of the duodenoscope to the bleeding areas. After a rapid and effective hemostatic response was successfully achieved, the procedure was terminated. Figure 3 shows an early bleeding during the endoscopic sphincterotomy, which has been controlled *via* the topical application of ABS.

Mallory-Weiss syndrome

Mallory-Weiss syndrome (MWS) was determined to be the cause of upper GI bleeding in 3%-10% of cases[51]. Bleeding in MWS usually stops spontaneously and patients can benefit from conservative medical treatment. Unfortunately, patients, especially those with stigmata of active

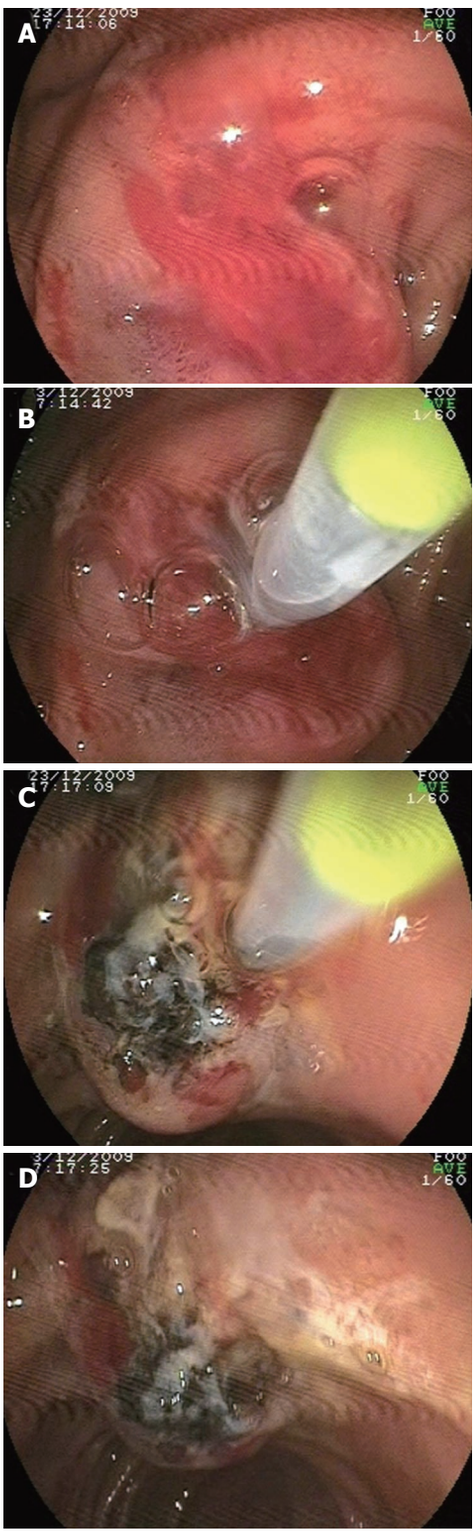

Figure 3 Ancaferd application during endoscopic sphincterotomy. A: Early bleeding during the endoscopic sphincterotomy; B: Ankaferd blood stopper (ABS) topically applied to the bleeding area; C: Hemorrhage was immediately controlled just after topical ABS administration; D: The bleeding site was covered by the hemostatic network related with the ABS application and hemorrhage was stopped.

bleeding and unstable vital signs at admission and/or associated co-morbid diseases, may require hemostatic intervention like hemoclip application, adrenaline injection and band ligation[52-54]. In a report by Ozaslan *et al*[35], a 62-year-old man with bleeding MWS was successfully treated with 13 mL of ABS. In another report, topical administration of ABS after unsuccessful combined endoscopic treatment in a warfarin-treated patient with bleeding MWS resulted in successful control after 7 mL of ABS application[22]. This case demonstrates the effectiveness of ABS even in patients receiving anticoagulant therapy, which could possibly broaden the use of ABS in distinct states of gastrointestinal bleeding with hemorrhagic diathesis.

Dieulafoy's lesion

Dieulafoy's lesion (DL) is an uncommon, but important, cause of upper gastrointestinal bleeding consisting of a submucosal ectatic artery in the gastrointestinal tract and has a high mortality rate when diagnosis and treatment are delayed. It accounts for 0.3%-6.7% of all causes of upper GI bleeding[55-57]. Endoscopic therapy is the current "standard-of-care" for patients with DL, because the lesions are commonly in an accessible localization with upper GI endoscopy[56]. Unfortunately, endoscopic therapy sometimes fails to control active bleeding, resulting in hemorrhagic shock, circulatory collapse associated with increased morbidity, and even mortality. The first experience with ABS in a 63-year-old patient with DL was reported by Kurt *et al*[21]. In a recent paper, ABS was also shown to be effective in bleeding DL as an adjuvant modality in two patients[22].

Variceal upper gastrointestinal bleeding

Variceal bleeding is one of the most serious and life-threatening complications of cirrhosis and portal hypertension, with mortality exceeding 50% in severe or advanced liver disease in acute variceal hemorrhage[42]. Gastroesophageal varices are present in approximately 50%-60% of patients with cirrhosis. The prevalence of variceal hemorrhage is approximately 5%-15% yearly, and early variceal rebleeding has a rate of occurrence of 30%-40% within the first 6 wk[29]. Despite urgent endoscopic and/or pharmacological therapy, variceal bleeding cannot be controlled, or recurs early, in about 10%-20% of patients with considerable morbidity and mortality rates[58]. Although, endoscopic band ligation (EBL) and sclerotherapy are the choice of endoscopic treatment modalities for both active variceal bleeding and for secondary prophylaxis, application difficulties during active bleeding necessitated a search for new techniques and agents that are effective and safe. Furthermore, ease of administration, not requiring much experience and non-toxicity (even if the endoscopist could not locate the exact bleeding site), and injecting ABS to the close proximity to the suspected bleeding area may stop the variceal bleeding immediately. For that reason, ABS seems to offer a practical alternative in the setting of gastroesophageal variceal bleeding. Recently Tuncer *et al*[14] reported a patient with a fundal variceal hemorrhage that was effectively treated with 6 mL of ABS. Immediate hemostasis was achieved in 18 s without any further treatment. Control endoscopy was performed on day 5 that revealed clean surface

Table 1 Current data regarding the use of Ankaferd blood stopper in distinct states of gastrointestinal bleedings

Reference	Year	*n*	Diagnosis	Mean ABS volume (mL)
Ibis *et al*[20]	2008	1	Solitary rectal ulcer	10
Kurt *et al*[21]	2008	1	Dieulafoy lesion	12
Kurt *et al*[42]	2008	1	Distal cholangiocellular carcinoma	15
Tuncer *et al*[14]	2010	1	Fundal variceal bleeding	6
Ozaslan *et al*[17]	2009	1	Radiation colitis	20
Kurt *et al*[43]	2010	3	Rectum cancer	5, 14
		7	Gastric cancer	7, 9
Ozaslan *et al*[44]	2010	5	Gastric cancer	8
		1	Periampullary cancer	10
Beyazit *et al*[13]	2010	1	Sphincterotomy bleeding	3
Ozaslan *et al*[15]	2010	1	Variceal bleeding	10
Karaman *et al*[16]	2010	5	Colonic postpolypectomy bleeding	5-6
		2	Gastric postpolypectomy bleeding	5-6
		1	Oozing visible vessel at duodenum	5
Shorbagi *et al*[18]	2010	1	Radiation proctitis	20
Ozaslan *et al*[19]	2010	8	Radiation proctitis	20-30
Kurt *et al*[22]	2010	6	Gastric postpolypectomy bleeding	10
		2	Duodenal postpolypectomy bleeding	5, 9
		3	Colonic postpolypectomy bleeding	3, 17
		4	Gastric biopsy	10
		2	Dieulafoy lesion	47
		3	Radiation colitis	24
		2	GAVE	15
		1	Congestive gastropathy	10
Ozaslan *et al*[35]	2010	5	Peptic ulcer	2, 7
		2	Acute erosive gastropathy	5
		1	Esophageal ulcer	7
		1	Mallory-Weiss	13
Purnak *et al*[36]	2011	1	Peptic ulcer	20
Zulfikar *et al*[46]	2011	1	Esophageal cancer	6

ABS: Ankaferd blood stopper; GAVE: Gastric antral vascular ectasia.

fundal varices and a successful variceal obscuration by cyanoacrylate injection that was performed subsequently. Similarly, in a case report by Ozaslan *et al*[15], a patient with alcoholic cirrhosis who developed severe bleeding during an elective EBL session due to immediate band slippage underwent endoscopic topical application of ABS, which was then associated with the cessation of the hemorrhage. Although both of these reports seem to be encouraging, further controlled randomized studies are required to validate the effectiveness of ABS in the therapy of gastroesophageal varices. Current data regarding the use of ABS in GI bleedings is summarized in Table 1.

LOWER GASTROINTESTINAL BLEEDING

Post-polypectomy bleeding

Bleeding following endoscopic polypectomy is the most common complication of colonic polypectomy[59], occurring in 0.3%-6.1% of polypectomies in various reports[60-62]. Bleeding can occur immediately following polypectomy or be delayed for hours or even up to 29 d[63]. Acute bleeding is due to the involvement of an underlying artery or inadequate coagulation of the polyp stalk and is usually self limiting, although active arterial bleeding can occur acutely.

The effectiveness of ABS for post-polypectomy bleeding was shown by Karaman *et al*[16] in 7 patients with post-polypectomy bleeding (5 cases of colonic, 2 cases of gastric polypectomy). ABS application was reported to be performed as a first choice in 5 cases, and after failed attempts with endoscopic interventions in 2 patients. Bleeding following polypectomy was stopped with ABS application in all of the cases without any other complication or re-bleeding. In a recent case series by Kurt *et al*[22], ABS application in a total of 11 patients (8 gastroduodenal, 3 colonic) with post-polypectomy bleeding resulted in the successful control of active bleeding.

Radiation colitis

Radiation proctitis (RP) is a relatively common late complication of pelvic radiation, commonly given for prostate, rectal, and gynecologic malignancies. The main symptoms of chronic RP are hematochezia (sometimes quite severe), urgency, constipation, tenesmus, diarrhea, and rectal pain. While mild cases may settle spontaneously over some months, severe hemorrhagic RP may required repeated blood transfusions and is difficult to treat with medical therapy such as sulfasalazine, corticosteroid enemas, and sucralfate (given orally or as an enema)[64,65]. Currently, argon plasma coagulation (APC) and local application of formalin are being used as main successful measures for therapy of RP, while APC treatment offers a safe non-contact method of delivering hemostasis compared to formalin[64-66]. Although complete healing of RP is not expected, even with APC or formalin, the measurement of efficacy with current treatments have been reported

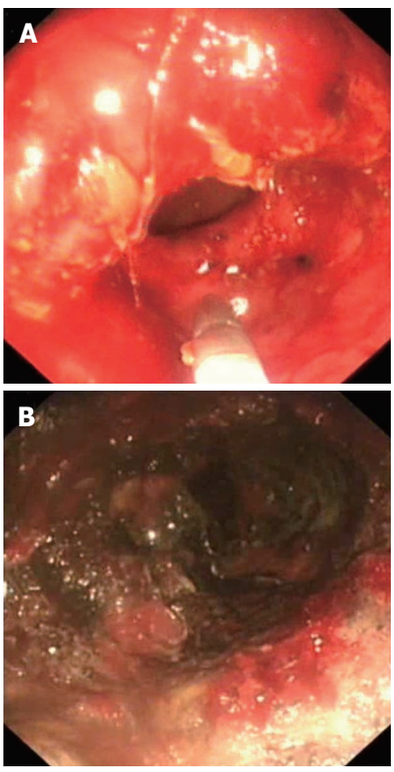

Figure 4 Endocopic images of the distal rectum in a patient with radiation proctitis. A: Before Ankaferd blood stopper (ABS) application with fresh bleeding; B: After ABS application with grayish-yellow coagulum formation covering the diseased area.

as decreased rectal bleeding, reduced transfusion requirement, improvements in endoscopic appearance and quality of life for the patients. In this setting, ABS may offer an exciting alternative in the treatment of RP, due to its ease of application, non-toxicity, and speed of action. It has a short procedure time and very simple technique (only spraying targeted or even just close to the bleeding area), and does not require expensive equipment like APC. Moreover, it offers two unique advantages to other modalities that are used in APC therapy; it doesn't requires precise localization of the site of bleeding when applied, and simple topical application over the whole lesion could suffice for the entire coating of the affected mucosa (Figure 4). The first case of successful ABS application in radiation colitis was reported by Ozaslan *et al*[17] in a 71-year-old woman who had undergone pelvic radiotherapy due to cancer of the cervix. A total of 20 mL ABS was used with a sclerotherapy needle on the lesion and resulted in a greyish-yellow discoloration of the affected mucosa with cessation of bleeding. Three further sessions were carried out on a weekly basis to complete the healing with no signs of re-bleeding in the following days. At follow-up, the giant ulcerated lesion was reported to have almost disappeared, with only mild residual erosions and friability remaining. A difficult case of radiation proctitis that was managed by ABS was also reported by Shorbagi *et al*[18] in a 70-year-old patient with failed management of both medical and endoscopic interventions with APC. In this report, approximately 20 mL of ABS solution was applied to the affected areas by using a disposable washing pipe, which resulted in the immediate control of bleeding. The authors concluded that ABS would be a useful adjuvant to APC since, by controlling the active bleed, it may help to better localize and target telangiectasias. Kurt *et al*[22] reported 3 patients with radiation colitis which was primarily managed with APC. Adjuvant application of ABS in these patients resulted in a more sustained control of bleeding. Aside from this reports, an observational study was also conducted in 8 patients with bleeding due to chronic RP in which ABS was applied as a primary therapy[19]. In this study, ABS was instilled onto the bleeding areas by sclerotherapy needle or heater probe catheter, once a week, at a dose of 20-30 mL per session. ABS-induced hemostasis lasted for 1-8 d per session, and was achieved in seven of eight cases. In the eighth case, bleeding was only lessened. However, recurrence of bleeding was seen in all patients and ABS was found to be ineffective on telangiectasia at the last follow-up. As a result, ABS was only found to be effective in healing radiation-induced ulcers with no prolonged effect on bleeding telangiectasias due to RP.

Based on current observations, ABS may lead to the apparent healing of ulcers, but it might not be useful for the healing of telangiectasia or as a definitive therapy for bleeding in patients with chronic RP.

Solitary rectal ulcer

Solitary rectal ulcer (SRU) is a rare rectal disorder that can be present with bleeding, passage of mucus, straining during defecation, and a sense of incomplete evacuation[67]. Although bleeding due to a rectal ulcer commonly stops spontaneously, re-bleeding is a major matter of concern, despite effective endoscopic interventions. Recently in a paper by Ibis *et al*[20], topical application of 10 mL of ABS onto the ulcer through a disposable washing pipe resulted in successful control of the bleeding. Furthermore, complete healing of a bleeding SRU located adjacent to the anal canal prevented a potential risk for infection with fecal passage.

Neoplastic lower gastrointestinal bleeding

Colon cancer is the predominant cause of neoplastic bleeding. It accounts for up to 2%-9% of cases of hematochezia and is, by far, the most frequent cause of iron-deficiency anemia and the source of chronic lower GI bleeding[68]. The bleeding is usually low-grade and recurrent, occurring as a result of erosions and ulceration on the surface of the tumor and often exacerbated by the use of NSAIDs. Although several endoscopic treatment modalities can be used to achieve hemostasis, when the bleeding tumoral lesion is identified in a colonoscopic examination, the majority of patients require surgical management due to increased re-bleeding rates, which can be as high as 80% up to 1 mo after the procedure. For that reason, alternative approaches are required, especially in inoperable cases or as a bridge to elective surgery. In this setting, ABS as a novel hemostatic agent could have a potential benefit in controlling bleeding from GI tumors. In a retrospective analysis, the effectiveness of ABS in lower GI bleeding due to rectal carcinoma was shown in three patients[43]. Hemostasis was achieved in all three patients

within seconds following ABS application, with no adverse events.

CONCLUSION

ABS, which has long been used as a traditional folkloric medicinal plant extract, represents an effective alternative treatment modality as a modern topical hemostatic agent for GI bleeding either as an adjuvant or primary agent complementing conventional methods. Although ABS is still in the early developmental stages as a drug, observations from published series with encouraging results provide evidence for the preliminary safety and efficacy of ABS in distinct states of GI bleeding as a haemostatic agent[13-22,35,42-46]. Future randomized controlled trials will elucidate whether ABS would be as much of a novel, safe and effective treatment option in the setting of GI bleeding.

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