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Endoscopic topical application of Ankaferd Blood Stopper for neoplastic gastrointestinal bleeding: A retrospective analysis

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ABSTRACT

Aim: The aim of this study was to retrospectively assess the haemostatic efficacy of the endoscopic topical use of Ankaferd Blood Stopper (ABS) in the setting of neoplastic GI bleeding.
Methods: The records of 10 patients with neoplastic GI bleeding (7 gastric, 3 rectal) were evaluated retrospectively. Written informed consent regarding the off-label use of ABS as a means of attaining haemostasis had been obtained from all of the patients prior to the procedure. In all patients, ABS was applied topically. Rates of bleeding control and post-procedural complications were documented.
Results: Haemostasis was achieved in all patients within seconds of endoscopic application of ABS, with no immediate complications. Seven patients underwent subsequent cancer surgery after a bleeding-free post-procedural period.
Conclusions: ABS as a novel haemostatic agent could have a potential benefit in controlling bleeding from GI tumours. Prospective controlled studies are needed to help establish its efficacy, and perhaps offer a comparison to conventional haemostatic interventions.

1. Introduction

Tumours are among the frequently encountered causes of GI bleeding, accounting to up to 5% of severe upper GI bleeding cases [1]. Severe bleeding is a bad prognostic sign for upper GI tumours, and endoscopic haemostatic interventions help offer a bridge to elective surgery. Various methods have been used to stop bleeding from gastroduodenal malignant lesions, including heater probe coagulation, injection of epinephrine, laser coagulation and injection of sodium tetradecyl sulphate with varying success rates (66–100%) [1,2]. However, these modalities were associated with rebleeding rates as high as 80% up to 1 month after the procedure.

Ankaferd Blood Stopper (ABS) is a standardised herbal extract obtained from five different plants *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum and Urtica dioica* [3]. The use of topical ABS has been approved by the Turkish Ministry of Health for the management of dermal, external post-surgical and post-dental surgery bleedings [3]. ABS manifests its unique haemostatic effect by promoting the formation of a protein network which acts as an anchor for vital physiological erythrocyte aggregation, covering the classical cascade model of the clotting system without independently acting on coagulation factors and platelets [3]. The in vivo haemostatic effect of ABS was evaluated in rats pretreated with acetylsalicylic acid or enoxaparine as well as in a swine model [4,5]. Data on the efficacy of ABS in GI system bleeding is limited to case reports [6–9]. The aim of this study was to assess the haemostatic efficacy of ABS solution for bleeding due to neoplastic GI disorders.

2. Materials and methods

2.1. Study design and patient selection

The medical records of all patients who underwent topical ABS application for GI bleeding at our institution between April 2008 and June 2008 were reviewed. A total of 10 patients had bleeding from neoplastic lesions (7 cases of gastric cancer and 3 cases of rectal cancer), either spontaneous or post-biopsy. Written informed consent regarding the off-label use of the ABS as means of attaining haemostasis was obtained from all patients prior to endoscopic procedures. Since ABS-induced haemostatic effect includes the formation of a protein network within vital erythrocyte aggregation covering the clotting system, its use was clinically indicated in all

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of the patients with signs of spontaneous tumoural or post-biopsy bleeding [3].

2.2. ABS application

Olympus® XQ20, 1T20 and Pentax® EG2940 diagnostic endoscopes were used for the topical application of ABS by disposable washing pipe (model: PW-205 L, Olympus corporation, Japan). The vials of ABS (Ankaferd Blood Stopper®; patent number 2007-0-114485 were provided by Ankaferd Drug Inc., Istanbul, Turkey (one vial of 50 ml).

3. Results

Retrospective analysis of the records of all patients disclosed that bleeding stopped within seconds of the application of topical ABS. A summary of patient characteristics, endoscopic findings and the dose of ABS used to control bleeding is depicted in Table 1. In case 1, multiple tissue biopsies were obtained from the lesion (Fig. 1B) and the ensuing bleeding was successfully controlled by topical administration of ABS. This produced greyish discolouration of the rectal mucosa (Fig. 1C). Fig. 1D depicts a picture of the mass which was obtained on a repeat colonoscopy 5 days later. All the other cases (with the exception of case 4) had spontaneous bleeding prior to biopsy. Post-biopsy oozing persisted in all cases, requiring haemostatic intervention. Due to the nature of the bleeding, ABS was the method preferred by the endoscopists.

All patients had a pathological diagnosis of adenocarcinoma. Seven of the cases who eventually underwent surgery at our hospital did not report rebleeding during the post-procedural period. Case 8 developed nausea and vomiting related to neoadjuvant chemotherapy, but again no signs of gastrointestinal bleeding.

4. Discussion

Primary gastrointestinal tumours, direct local invasion by other malignancies, and metastatic disease to the gastrointestinal tract can all cause gastrointestinal bleeding, which is rarely massive and seldom causes haemodynamic instability. However, cancer patients may be on anticoagulation for deep venous thrombosis or pulmonary emboli or may be coagulopathic, and therefore bleeding may be more severe necessitating frequent transfusions and ongoing hospitalisation.

Endoscopic haemostasis in this setting is often a temporary measure prior to staging and surgical resection. There is no consensus on the best endoscopic treatment modality for bleeding gastrointestinal tumours. Injection therapy, thermal contact probes (tumour probe, bipolar probes, or heater probe), and laser therapy are often not practical or useful, and varying levels of success have been reported [1,2]. Endoscopic treatment may slow or stop the bleeding temporarily, but recurrent tumour bleeding is likely, and endoscopic management rarely, if ever, impacts on overall survival, as the majority of patients die within 12 months. If gastrointestinal tumour bleeding is brisk, angiography and embolisation can be considered, but such bleeding is rarely rapid enough for them to be successful. Depending on the location of the bleeding and the overall prognosis of the patient, palliative surgery may be an option. This approach is rarely practical, however, because of the morbidity of the surgical procedure. Palliative radiation therapy may also be considered as another alternative [10].

In the setting of malignant GI bleeding, ABS was used previously in a patient with major GI bleeding from a recurrent lesion at the hepaticojejunostomy anastomosis following surgery for distal cholangiocellular carcinoma [6]. A submucosal injection of 1:10,000 epinephrine and argon plasma coagulation failed to completely control the bleeding. This was followed by application of ABS which achieved haemostasis within seconds. He presented 2 months later with recurrent bleeding and underwent surgery for relapse.

ABS is still in the early stages of possibly establishing itself as a haemostatic agent for gastrointestinal bleeding, and several studies on its safety and efficacy are still ongoing. It would seem, as from the case above, that ABS may have a role as an adjuvant to conventional modalities, particularly for major tumoural bleeding. Moreover, the data from our study indicates that ABS may be useful as a stand-alone haemostatic endoscopic intervention for oozing gastrointestinal tumoural bleeding. ABS may offer an exciting option due to the ease of application and speed of action. It offers an advantage to other modalities as it does not require precise localisation of the site of bleeding. Simple topical application

Table 1
Patient characteristics, haemoglobin levels, the dose of ABS to control bleeding and time to surgery.

No.	Age/sex	Associated disease/drug	Complaint	Hb (g/dL)	Endoscopic finding	ABS (ml)	Time to surgery (day)
1	73/F	DM, HT/ASA	Rectal bleeding for 4 months	13.2	A polypoid bleeding mass at 8 cm from the anal verge (Fig. 1A)	19	48
2	81/M	–/ASA	Haematemesis for 3 days	7.4	Ulcerated, bleeding lesion, and 4 cm in diameter, at the gastric angulus	15	20
3	78/F	HT, CHF	Rectal bleeding	13.5	A 3.5 cm × 4 cm semipedunculated haemorrhagic, polypoid mass in the rectum	3	10
4	67/F		Abdominal pain and vomiting	11.9	An annular ulcerative vegetated lesion involving almost the entire pylorus	14	n/a
5	55/F		Epigastric pain	13.0	A haemorrhagic, fragile, ulcerative mass in the cardia of stomach	15	n/a
6	62/M		Weight loss and difficulty in swallowing	14.0	Extensive, irregular, haemorrhagic, fragile, lesion in the cardia and corpus of the stomach	12	16
7	56/F	Hyperthyroidism	Haematemesis for 2 months	9.2	A bleeding, fragile mass arising from the greater curvature of the stomach and extends to the incisura angularis	6	7
8	63/M	DM	Weight loss and difficulty in swallowing	13.6	An ulcerated bleeding mass involving the cardia and gastroesophageal junction	9	Neoadjuvant chemotherapy
9	45/F		Epigastric pain and weight loss	n/a	An annular ulcerative lesion involving the entire pylorus and prepyloric antrum	9	22
10	48/F		Rectal bleeding for 1 year	11.4	A vegetative haemorrhagic mass at 3 cm from the anal verge	10	12

Abbreviations: ASA: acetylsalicylic acid; CHF: congestive heart failure; DM: diabetes mellitus; F: female; Hb: haemoglobin; HT: hypertension; M: male.

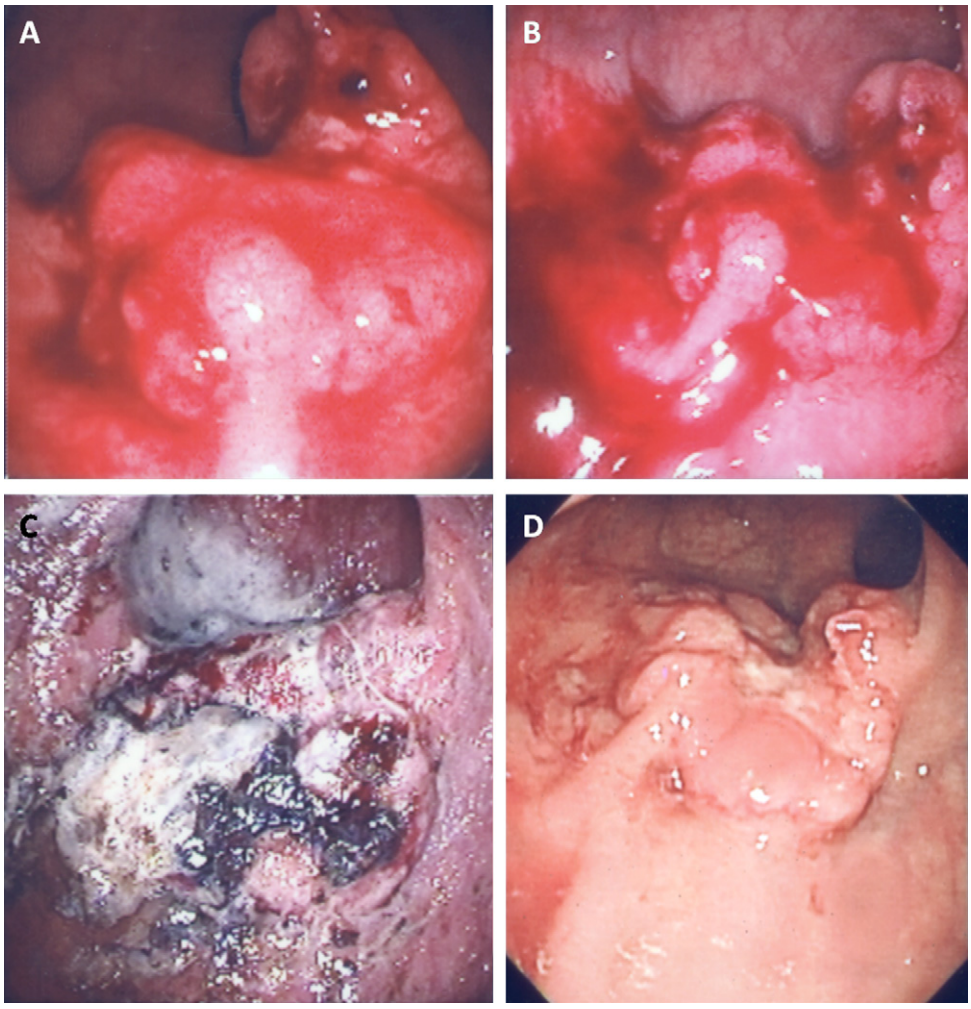

Fig. 1. Endoscopic application of ABS for a bleeding rectum cancer in case 1; A: before and B: after the rectal biopsy; C: haemostasis was achieved after application of ABS solution; D: 5 days later, endoscopic appearance of nonbleeding rectal mass.

over the whole lesion could suffice, and perhaps help localise the bleeding for the subsequent use of other methods of haemostasis such as sclerotherapy or heater probe.

The effective management of the bleeding problem is also evident in patients with the use of anticoagulant and antihaemostatic drugs [11]. Successful endoscopic therapy at rates comparable with those achieved in non-anti-coagulated patients was previously reported by Choudari et al. [12] But in bleeding cancer patients, having a local primary haemostatic defect as well, anticoagulation might cause a therapeutic challenge. In cases 1 and 2 using ASA, ABS effectively stopped bleeding. This observation also supported the idea that the effect of ABS is not dependent on coagulation factors and platelet function.

It is well known that angiogenesis is stimulated during oncogenesis. The newly formed vasculature does not have a normal stroma and predisposes to bleeding. The infiltration of the wall of the normal vasculature by tumoural elements also interferes with the primary haemostasis. For these reasons the high rebleeding rates in patients with tumours is understandable. Because ABS has a potential to be effective in patients with deficient primary haemostasis it might have a widespread use in these patients in the future.

The antiangiogenic and antitumour effects of the plants within the content of the drug may also contribute to the effect of this drug in the setting of tumoural bleeding [3]. Periodical histological monitorisation of the macroscopic alterations in the tumour tissue after the administration of ABS shall be performed in upcoming controlled prospective studies. On the other hand, coagulum formed by the rapid coagulation of the blood together with the colour changes may cause problems in detecting the bleeding lesion. So the drug must be applied after precisely locating the exact site of oozing blood. No adverse systemic effect was detected after the administration of the medicinal product. During the local administration of ABS a local macroscopic dirty-white discolouration is observed. But in case 1, we later saw that it disappeared.

5. Conclusion

It is still early days for ABS as a dependable haemostatic agent for GI bleeding, as research on the molecular basis of Ankaferd's mechanism of action has only recently been published [13]. There is a dire need for controlled studies before it can establish itself as a novel, safe and effective treatment option in the setting of GI bleeding.

Conflict of interest statement

The author(s) indicated no potential conflicts of interest.

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