Case Reports

New Coagulant Agent (Ankaferd Blood Stopper) for Open Hemorrhages in Hemophilia With Inhibitor

Ahmet Faik Öner, MD, Murat Doğu, MD, Avni Kaya, MD, Ertan Sal, MD, Mehmet Selçuk Bektaş, MD, Osman Yesilmen, MD, Harun Ayhan, and Mehmet Acikgoz, MD

The treatment of hemophilia A patients with inhibitor could be very expensive. Ankaferd blood stopper (ABS) is a unique folkloric medicinal plant extract, which has historically been used in Turkish traditional medicine as a hemostatic agent. In this article, a 16-year-old boy was presented with uncontrolled bleeding, despite the treatment of factor VIII, rVIIa, factor VIII inhibitor bypass activity (FEIBA), cyclophosphamide, and prednisolone at circumcision site that resolved with ABS in minutes. Our patient with hemophilia A and inhibitor is the first clinical pediatric case.

Keywords: Ankaferd blood stopper; hemophilia A; inhibitor

Introduction

Inhibitor development in hemophilia A patients is one of the major complications during therapy. Therapeutical approach in hemophilia A patients with inhibitor is a crucial problem. Ankaferd blood stopper (ABS) is a new therapeutic agent, which is derived from 5 different herbal extracts, and can stop bleeding within minutes in all type of open hemorrhages. Ankaferd blood stopper is available in ampoule, tampon, and spray form. In this article, a 16-year-old boy with uncontrolled bleeding despite the treatment of factor VIII, rVIIa, factor VIII inhibitor bypass activity (FEIBA), cyclophosphamide, and prednisolone at circumcision site that resolved with ABS in minutes was presented. Our patient with hemophilia A and inhibitor is the first clinical pediatric case where ABS was used.

Case Report

A 16-year-old boy diagnosed with hemophilia A referred to our hospital due to bleeding complaint after circumcision. It was learnt that the circumcision operation had been conducted 2 days ago in another center together with his brother who is also a hemophilia A patient. Although hemorrhage was monitored in his brother, the uncontrolled bleeding had been observed in our patient. Factor VIII had been administered before and after the circumcision at a dose of 50 U/kg per dose. However, bleeding had not stopped and then the patient was immediately referred to our hospital. In his history, it was learnt that hemophilia A diagnosis was made at 4 years old and in that time, his prothrombine time was measured as 13 seconds (normal range: 11-14 seconds), active partial thromboplastin time (aPTT) as 80 seconds (normal range: 26-38 seconds), and factor VIII level as 1% (normal range 70%-100%). Other coagulation factors’ levels were in normal range. From that time, factor VIII preparations have been administered several times due to gingival bleeding, hemarthrosis, and hematuria. Inhibitor positivity was determined when he was 12 years old.
On physical examination, a blood pressure was measured as 100/60 mm Hg, a body weight as 40 kg. The other vital signs were normal. Other physical examination findings were normal, except the bleeding (blood leakage) at the circumcision site. Laboratory findings showed markedly decreased FVIII activity (1%, normal range 70%-100%), prolongation of coagulation time aPTT 90 seconds (normal range 26-38 seconds) and anemia 8 g/dL (normal range 12-16 g/dL). Factor VIII inhibitors were detectable at 6.4 Bethesda Units (BU). All other immunological serum parameters (eg, antinuclear antibodies, extractable nuclear antigens, and the Coombs test) were negative. A factor VIII therapy of 50 U/kg per 8 hours was initiated to the patient. Bleeding did not stop and the current treatment was elevated to 100 U/kg per 8 hours. The total amount of factor VIII administered to the patient was totally 95,000 U/5 days (3 doses in a day). In the meantime, rVIIa (totally 20 mg/2 days) and then FEIBA (totally 18,000 U/3 days, 150 U/kg per day) were given to him. In addition, cyclophosphamide and prednisolone were also administered as other treatments. Spite of these treatments, hemorrhage did not stop. Erythrocyte suspension transfusion was given to him 2 times. The condition was explained to the parent of the patient, and a written consent document was obtained before ABS (Ankaferd Health Products Ltd, Istanbul, Turkey) was used on eighth day of hospitalization. Bleeding entirely stopped within few minutes after ABS was applied to the surface of the bleeding site once only. The patient, who had no bleeding events during follow-up, was discharged from the hospital and recommended to visit the hospital for follow-up. Our patient with hemophilia A and inhibitor is the first clinical pediatric case where ABS was used.

Discussion

Ankaferd blood stopper, a standardized mixture of 5 plants (Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica), has historically been used in Turkish traditional as a hemostatic agent but its mechanism of action remains unknown.2-9 Goker et al2 designed a study to investigate the in vitro effects of ABS on hemostatic parameters. When added to plasma or serum, ABS induced the very rapid formation of a protein network and erythrocyte aggregation. They found that ABS did not affect factors II, V, VII, VIII, IX, X, XI, and XIII, but it decreased the plasma fibrinogen activity and antigen levels. Their findings suggest that the basic mechanism of ABS is the formation of an encapsulated protein network that provides focal points for aggregation of red blood cells.2 In addition, they observed that the addition of ABS to normal plasma and serum resulted in the very rapid (<1 second) formation of a protein network.2 Cipil et al15 designed a study to evaluate in vivo hemostatic effect of ABS in rats pretreated with warfarin. They found that ABS was beneficial as a topical hemostatic agent in bleeding rats. Interestingly, they observed that ABS showed its hemostatic action not only in the untreated animals but also in the animals pretreated with warfarin. In addition, they showed that ABS has showed its hemostatic effect via modulation of the platelet functions.3 In conclusions, they emphasized that ABS had in vivo hemostatic actions that may provide a therapeutic potential for the management of patients with deficient primary hemostasis in clinical medicine.3

In addition to these reports, the in vitro antimicrobial activity of ABS was assessed on 102 clinical isolates from both gram-negative and gram-positive bacteria by Tasdelen Fisgin et al4. They found that ABS was significantly active against all bacteria investigated.4 Therefore, ABS is currently being studied in the treatment of Kirim-Kongo hemorrhagic fever with promising preliminary results, based on its anti-infective and hemostatic efficacy.8,9

With these studies, 3 different articles were published in literature. First, Kurt M et al15 presented a case report about endoscopic application of ABS as a novel experimental treatment modality for upper gastrointestinal bleeding. Then, Ibis et al6 published an article about successful management of bleeding due to solitary rectal ulcer via topical application of ABS. Kurt et al7 reported a different case about ABS as an effective adjunctive hemostatic agent for the management of life-threatening arterial bleeding of the digestive tract again. All the patients mentioned above were adults, and none of them had hemophilia A with inhibitor. Our patient with hemophilia A and inhibitor is the first clinical pediatric case where ABS was used.

Inhibitor development in hemophilia A patients is one of the major complications during therapy. Therapeutical approach in hemophilia A patients with inhibitor is a crucial problem. Existing treatments for hemophilia A patients with inhibitor are continuous high-dose factor VIII infusion, recombinant active factor VII, and active prothrombin complex preparations.1,10 Epsilon amino caproic acid,
desmopressin, thrombocyte concentrates, steroids, cyclophosphamide preparations, and plasmapheresis can be used in unresponsive cases, with these treatments mentioned above.\textsuperscript{11-14} The treatment of hemophilia A patients with inhibitor can be very expensive with these treatments. In refractory cases, treatment with a chimerical monoclonal anti-CD20 antibody (rituximab)\textsuperscript{15} or 2-chlorodeoxyadenosine (2-CDA)\textsuperscript{16} was reported to be successful. While in hemophilia A, low titer inhibitors (<5 BU/mL) may be overcome by higher doses of human FVIII concentrates; this approach does not seem to be effective in patients with higher antibody titer (>10 BU/mL). In our case, factor VIII was administered to the patient at 95,000 U/5 days, the total amount of rVIIa was 20 mg/3 days, and the total amount of FEIBA was 18,000 units/3 days. Spite of these treatments, hemorrhage did not stop. Additionally, even though other treatments such as cyclophosphamide and prednisolone were used, bleeding did not stop. Finally, ABS was used. Bleeding entirely stopped within few minutes after ABS was applied to the surface of the bleeding site once only. The patient, who had no bleeding events during follow-up, was discharged from the hospital and recommended to visit the hospital for follow-up. Our patient with hemophilia A and inhibitor is the first clinical pediatric case where ABS was used.

**Cost-Effectiveness**

In the elapsed time until ABS used, the total amount of factor VIII, administered to the patient, was 95,000 U, rVIIa was 20 mg, and FEIBA was 18,000 units. The total cost of factor VIII, rVIIa, and FEIBA in Turkey were approximately US$50,000, US$15,000, and US$15,000, respectively. Nevertheless, ABS cost only approximately US$150. In addition, in our patient, bleeding entirely stopped within few minutes after ABS was applied to the surface of the bleeding site once only. Therefore, we think that ABS may be attempted for externally open and superficial injuries in patient with hemophilia A and/or inhibitor before the expensive treatments due to cost-effectiveness.

**Conclusion**

In conclusion, we think that ABS will bring a cheap and practical solution to solve this problem, especially in patients with hemophilia with externally open and superficial injuries. The antibacterial activity of ABS provides additional advantage to using this agent on open and superficial injuries such our case. Controlled, large-scaled researches should be performed to understand whatever ABS is a useless extract or a miracle.

**References**


For reprints and permissions queries, please visit SAGE’s Web site at http://www.sagepub.com/journalsPermissions.nav