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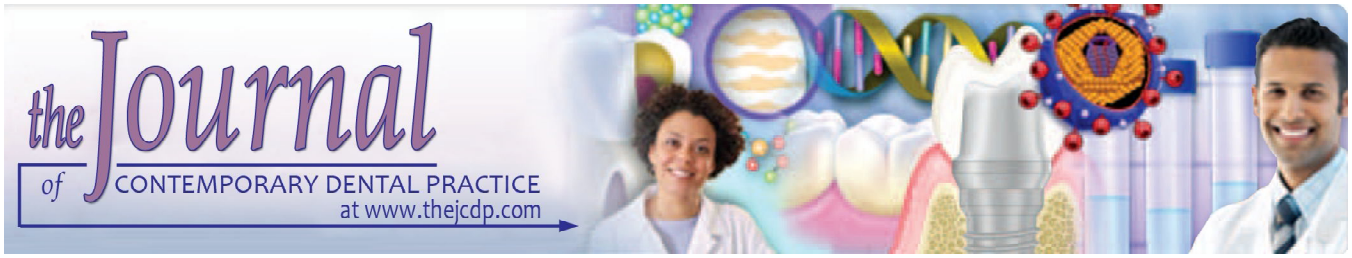
ORIGINAL RESEARCH



Successful Management of Bleeding after Dental Procedures with Application of Blood Stopper: A Single Center Prospective Trial

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ABSTRACT

Aim: Ankaferd Blood Stopper (ABS), as an herbal complementary medicine, has been approved for the management of clinical hemorrhages in Turkey, including dental interventions. Basic, preclinical and clinical studies disclosed the settings of the topical hemostatic use of ABS. The aim of this study is therefore to assess the efficacy and safety of ABS as an antihemorrhagic agent in the bleedings associated with dental procedures in patients with normal and impaired hemostasis.

Materials and methods: ABS has been topically applied by homogeneously spraying to the 113 patients during dental interventions within its on-label indications. A median of 0.5 ml (IQR:0.5-1 ml) ABS was administered after tooth extraction with prolonged hemorrhages.

Results: After the administration, bleeding stopped in less than 10 seconds in 59 (52.2%) patients, and below 22.5 seconds (IQR: 18, 8-30) in 54 patients (47.8%). A total of 141 procedures were performed in these 113 patients, and nearly 72.5 ml ABS was used with a total cost of 98 €.

Conclusion: ABS as a new herbal medicine was found to be an effective method for controlling bleeding related to dental procedures. No patient had wound infection and the healing process appeared to be normal. Topical ABS could be useful for the local hemostasis and wound healing in periodontal surgeries.

Clinical significance: In this prospective study ABS, for the first time, has demonstrated its potential for being an effective hemostatic agent for the management of bleedings due to dental procedures.

Keywords: Ankaferd, Bleeding, Dental surgery, Hemostasis.

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INTRODUCTION

Ankaferd Blood Stopper (ABS) is a unique medicinal plant extract, which has historically been used in Turkish traditional medicine as a hemostatic agent. ABS has been approved for the clinical management of external hemorrhage, postsurgical and postdental surgery bleedings in Turkey.[1-3] ABS also has the therapeutic potential to be used for the management of hemorrhages in difficult clinical conditions.[4-6] ABS contains a standardized mixture of the plants *Thymus vulgaris, Vitis vinifera, Glycyrrhiza glabra, Alpinia officinarum* and *Urtica dioica* (Table 1). ABS represents its unique hemostatic effect by inducing a very rapid (<1 second) structure of a protein network, which acts as an anchor for vital physiological erythrocyte aggregation, covering the classical cascade model of the clotting system without disturbing individual coagulation factors and platelets (Fig. 1).[1,2] ABS also upregulates the GATA/FOG transcription system affecting erythroid functions and urotensin II. These concepts have been developed via MALDI-TOF proteomic molecular analyses, cytometric arrays, transcription analysis and scanning electron microscopy (SEM) examinations (Figs 2A and B) as well as numerous investigations interacting with *in vitro* and *in vivo* research settings.[1]

Physiological cell-based coagulation could be achieved clinically by topical ABS application to prevent and treat bleeding in many distinct clinicopathological conditions.[7-12] Neither local nor systemic adverse effect and/or toxicity has been observed in association with the use of ABS in the experimental and anecdotal topical applications.

Exaggerated bleeding, mainly in patients with hereditary or acquired hemorrhagic diathesis, is a challenging issue

Table 1: Ingredients of spray, ampoule and pad forms of Ankaferd Blood Stopper®

Name of the active substance	*Amount of the active substance*				
	Spray (mg/ml)	*Ampoule (mg)*		*Pad (mg)*	
Size of vehicle		2 ml	2.5 × 7 cm 3 ml	5 × 7.5 cm 10 ml	20 × 20 cm 100 ml
Urtica dioica[1]	0.06	0.12	0.18	0.6	6
Vitis vinifera[2]	0.08	0.16	0.24	0.8	8
Glycyrrhiza glabra[2]	0.09	0.18	0.27	0.9	9
Alpinia officinarum[2]	0.14	0.14	0.21	0.7	7
Thymus vulgaris[3]	0.10		0.15	0.5	5

[1]*Dried root extract,* [2]*dried leaf extract,* [3]*dried grass extract*

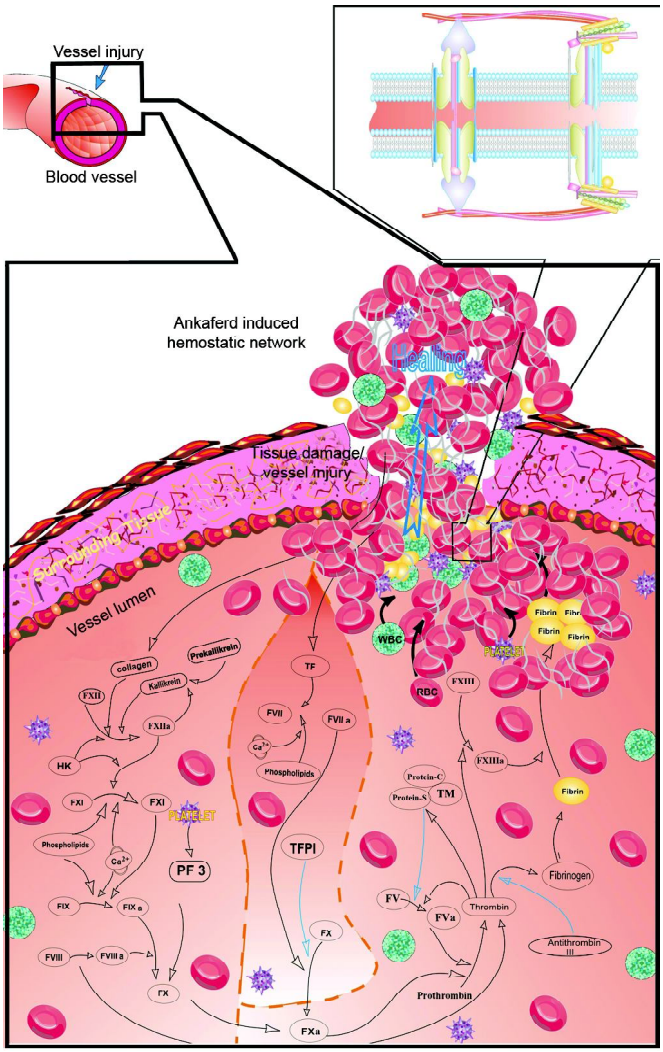
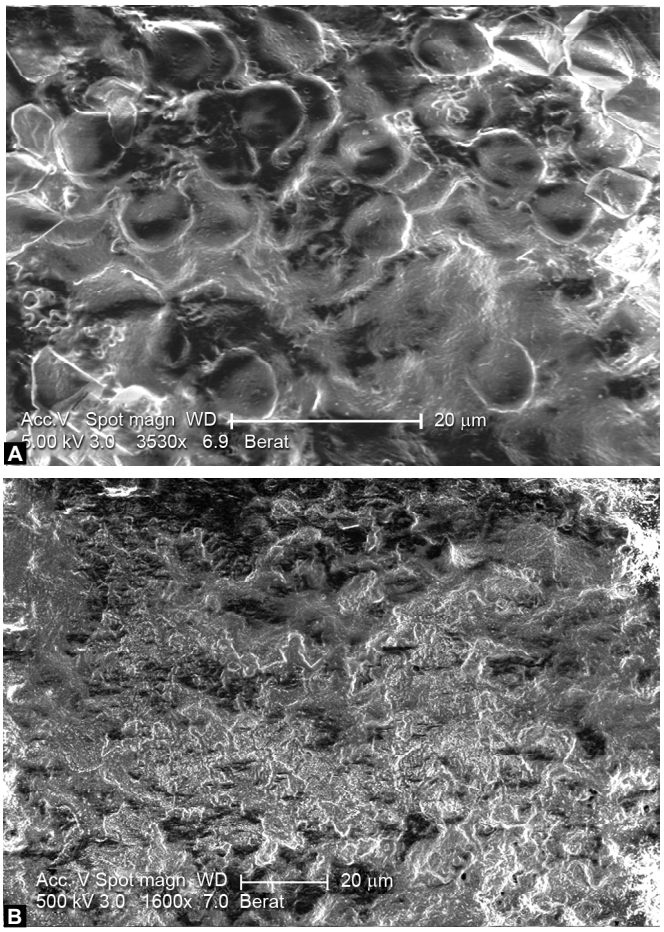


Fig. 1: The basic mechanism of action for Ankaferd Blood Stopper (ABS) is the formation of an encapsulated protein network that provides focal points for erythrocyte aggregation. ABS-induced formation of the unique protein network within the vital erythroid aggregation covers the entire physiological hemostatic 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 ATP bioenergy are included in the protein library of Ankaferd (Modified from Beyazit et al 2010, with permission)



Figs 2A and B: (A) Scanning electron microscopy images of whole blood cells prior to ABS application and (B) after ABS application

for the dental profession on a daily practice, therefore, ABS may be useful both in individuals with normal hemostatic parameters and in patients with deficient primary hemostasis and/or secondary hemostasis.[1-3] After the authorization of ABS for the management of dental bleeding by Ministry of Health of Turkey, ABS has been added to the protocols of prevention and treatment of prolonged hemorrhage due to dental procedures. The aim of this study is to assess the efficacy and safety of ABS as an antihemorrhagic agent in

the bleedings associated with dental procedures in patients with normal and impaired hemostasis.

MATERIALS AND METHODS

The study population consisted of 113 patients (63 women, 50 men; median aged 38 years) who had a prolonged bleeding (> 45 seconds) after a dental intervention regardless of the underlying illness. Topical anesthesia was achieved by Ultracaine-DS® ampoule (40 mg of Articain HCL, 0.006 mg /ml of Epinephrine HCL), whereas Citanest® flacon (2% prilocaine) was preferred for patients with type II diabetes and hypertension. The dental problems that urged the patient to apply to the clinic, drug use and the distribution of the associated systemic diseases were depicted in Table 2. Dental interventions performed to study participants were summarized in Table 3. ABS has been topically applied by homogeneously spraying with a high pressure to the cavity. Bleeding time was measured from the time of incision to cessation of free-flowing blood from the incision. Side effects which could possibly be related to ABS application were also noted. The study was conducted in accordance with the guidelines of Helsinki declaration. Each participant gave informed consent for the study.

Table 2: Characteristics and distribution of the associated systemic diseases of the study participants

Patient characteristics		*n*
Total number of patients		113
Male/female		50/63
Age (median)		38 (9-77)
Associated diseases	Diabetes mellitus	7
	Hypertension	15
	Coronary artery disease	6
	Hypothyroidism	1
Drugs	Acetylsalicylic acid	9
	Coumadin	3

Data analysis was performed using statistical package for social sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, United States). Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Values were presented as mean ± standard deviations or in the case of nonnormally distributed data, as median and interquartile range. Comparisons of percentages between groups of patients were carried out using the chi-square test. All normally-distributed data were analyzed using unpaired Student t-test. Data found to be nonnormally distributed were analyzed using the nonparametric Mann-Whitney U test (for 2 groups). A p-value of < 0.05 was deemed statistically significant.

RESULTS

The patients were administered median 0.5 ml (IQR: 0.5-1 ml) of ABS. Local anesthesia was performed to all patients. After ABS administration, bleeding stopped in less than 10 seconds in 59 (52.2%) patients, and below 22.5 seconds (IQR: 18, 8-30) in 54 patients (47.8%). A total of 141 procedures were performed in these 113 patients, and nearly 72.5 ml ABS was used with a total cost of 98 €. Neither of the patients needed a second dose of ABS. No patient had wound infection and the healing process appeared to be normal. Thirty patients reported a metallic taste in the mouth lasting 2 to 6 minutes. Two patients had oral numbness and the feeling of the mouth being stretched that recovered within 10 minutes.

The international normalized ratio (INR) and activated partial thromboplastin time (aPTT) values were normal for all the patients before the dental procedure except for three patients using warfarin. The baseline INR values of these three patients were 2.1, 1.9 and 1.85 and the bleeding stopped in 25, 37 and 40 seconds respectively after ABS administration to these patients. There was no difference between the pre- and posttreatment values of INR, aPTT, prothrombin time and fibrinogen in the other 110 patients evaluated. The treatment had no effect on the blood cell counts and other parameters of hematological analysis.

DISCUSSION

In the present study, we examined the safety and efficacy of local ABS application to manage prolonged bleeding following dental procedures in patients with normal and impaired hemostasis. ABS is found to have high hemostatic efficiency in prolonged dental bleedings. The herbal hemostatic agent reduced the need for additional medications and interventions as well as the cost of treatment.

Exaggerated bleeding episodes which can result from hereditary or acquired alterations in blood vessels, platelets, clotting factors or in the fibrinolytic system, is a challenging problem in dental clinics on a daily basis. Conventional treatment of patients with antithrombotic, procoagulant and antifibrinolytic medications is frequently used for the management of difficult bleedings. Ankaferd-induced formation of the protein network covers the whole physiological hemostatic process without unequally affecting any individual clotting factor in many pathobiological conditions.[1] ABS may, therefore, be effective both in individuals with normal hemostatic parameters and in patients with deficient primary hemostasis and/or secondary hemostasis. The present clinical study

Table 3: Dental interventions performed to study participants

Procedures		*n*	*%*
Tooth extractions	***Uncomplicated extractions***		
	Central incisor	15	8
	Lateral incisor	15	8
	Canine	2	1.1
	First premolar	2	1.1
	Second premolar	7	3.6
	First molar	11	5.8
	Second molar	12	6.3
	Third molar	43	22.9
	Complicated extractions		
	Apeks extraction		
	First premolar	2	1.1
	Second premolar	7	3.6
	Second molar	1	0.6
	Broken tooth		
	Third molar	3	1.6
	Sinus perforation		
	First molar	2	1.1
	Extractions with mucosa retention		
	Second molar	1	0.6
	Third molar	19	10
	Extractions with bone retention		
	First premolar	1	0.6
	Third molar	17	8.9
Small surgical procedures	Oral papilloma	3	1.7
	Apical periodontal cyst	6	3.2
	Large odontogenic cyst	1	0.6
	Fibroma	4	2.1
	Torus mandibularis	2	1.1
	Sinus surgery	2	1.1
	Alveoloplasty	8	4.2
	Apical resection	2	1.1

*Since most patients had exposed to more than one extraction, the total number of the extractions exceeds the total number of patients (n=113) who had tooth extraction

confirmed the efficacy of ABS to achieve homeostasis in external hemorrhage. Also, our results show that indications of ABS as a promising hemostatic agent may be expanded for use in other bleeding models, including skin, visceral, arterial, and venous injury in the near future. In a recent study, Al B et al[13] showed the effectiveness of ABS in the topical control of active bleeding due to cutaneous-subcutaneous incisions. And also in various clinical studies, ABS was also found to be effective in controlling in gastrointestinal bleedings and decreasing tumor vascularization.[9-12,14] In a prospective, controlled clinical trial of ABS in children undergoing tonsillectomy showed a decrease in intraoperative bleeding and operating time, as compared to the traditional hemostasis methods after cold knife dissection tonsillectomy.[15]

Hemostatic failure characterized by a tendency to bleeding or thrombosis, constitute a serious challenge in the dental practice and one of the most serious problems encountered by the dental professionals. It may cause prolonged postoperative bleeding, delay in wound healing and increase risk of infection.[3] When dental treatment is planned, several aspects relating to the care of such patients must be recognized and taken into consideration. Although the risks of hemorrhage are directly associated with the kind of procedure and the etiology of the underlying bleeding disorder, these patients should be referred to a hematologist for evaluation before dental intervention.

The dental management of patients with bleeding disorders must take into consideration not only the nature and severity of the disorder but also the type, location and extent of the procedure. Management strategy then depends on a fusion of the local and systemic considerations.[16] Local hemostatic measures, such as fibrin glues, oxidized cellulose, nonresorbable sutures, replacement therapy with clotting factor concentrates, antifibrinolytic agents and desmopressin which induces the release of factor VIII and von Willebrand's factor are the current mostly used treatment modalities in patients with bleeding disorders.[17-22] Unfortunately some of these methods (e.g. replacement therapy with clotting factors) inevitably carries potential risks for viral infection transmission and the formation of inhibitors to clotting factors.[21]

ABS is a unique medicinal plant extract induces very rapid formation of a protein network in the plasma and serum

samples.[1,2] Blood cells, particularly erythrocytes aggregate rapidly (< 1 second) in the presence of ABS and they are involved in the network formation. Individual coagulation factors are not affected during this antihemorrhagic process.[1,2] ABS acts independently of the classic coagulation cascade and contribute to the wound healing process. The antiinfectivity action of ABS had been demonstrated *in vitro* and ABS also had been used topically for the management of hemorrhages uncontrolled by standard measures in a wide variety of difficult clinical conditions.[9-12,23,24] In our study, hemostasis was accomplished in all of 113 patients. In three patient using warfarin and nine patients using ASA, ABS effectively stopped bleeding. Based on the effectiveness of ABS even in patients with defective hemostasis, it is reasonable to suggest that the effect of ABS does not require an intact coagulation system. Moreover, ABS can be effective in patients with platelet function abnormalities. Although no systemic toxicity was noted in our patients regarding to ABS application, we noticed a local macroscopic dirty-white discoloration in the dental areas that ABS was administered. This local discoloration disappeared in a short period of time.

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CONCLUSION

Based on our experience of 113 cases in which ABS was successfully applied, we think that ABS represents a promising alternative treatment modality for bleedings related to dental procedures. The ability of ABS to induce local hemostasis with protein network formation not only makes it an effective hemostatic agent but also confers anti-infective, and healing modulator properties which is also crucial for periodontal interventions.

CLINICAL SIGNIFICANCE

In this unique prospective trial, the potential of ABS as an effective hemostatic agent for the management of bleedings due to dental procedures were successfully demonstrated. Future controlled trials are needed to shed further light on the expanding spectrum of ABS effects in hemostasis in the setting of dental interventions.

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