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Prospective, randomized, controlled clinical trial of Ankaferd Blood Stopper in patients with acute anterior epistaxis

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Abstract This is a study evaluating the efficacy of Ankaferd Blood Stopper (ABS) as a hemostatic agent compared to hemostasis by phenylephrine in patients with anterior epistaxis. The study design is a prospective, randomized, controlled, nonblinded, clinical trial. In total, 49 patients were randomly seperated to receive hemostasis technique by means of either ABS wet tampon or phenylephrine impregnated gauze tampon for anterior epistaxis control. Patients were crossed over to the other technique after two unsuccessful attempts of the first technique. Measured outcomes such as number of applications, relationship of number of applications with bleeding intensity (1 = stains on napkin, 2 = soaked napkin, 3 = bowl needed), patient discomfort during hemostasis (0 = none, 9 = unbearable), and complications were assessed. Additional data were recorded for rebleeding within 7 days. 24 of the 49 patients were assigned to the new ABS group (group I) and remaining 25 were included in the standard phenylephrine group (group II). ABS was more effective than phenylephrine at control of anterior epistaxis (79.2 vs. 64%, $p < 0.05$). For the patients who crossed over from phenylephrine to ABS, 44.4% achieved hemostasis by ABS. ABS successfully treated all bleeding intensity 1 and 2 patients with one application (5 min). ABS patients experienced fewer rebleeding rates within 7 days compared to phenylephrine patients (8.3 vs. 20%, $p < 0.05$). The patients for which ABS was applied, significant differences in effective control of anterior epistaxis were observed compared to phenylephrine. ABS is effective, safe, quick, and easy alternative to the phenylephrine in patients with anterior epistaxis.

Keywords Epistaxis · Ankaferd Blood Stopper® · Hemostasis · Phenylephrine

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Introduction

Epistaxis, active bleeding from the nose, is a common ear, nose and throat emergency, and can be severe or even fatal. The causes can be from local or systemic illnesses. Epistaxis is classified as anterior or posterior on the basis of the primary bleeding site. Hemorrhage is most commonly anterior, originating from the nasal septum. A common source of anterior epistaxis is the Kiesselbach plexus, an anastomotic network of vessels on the anterior portion of the nasal septum [1].

Hemorrhage from this region can usually be managed by applying pressure to the nostrils, chemical or electro cauterization, topical hemostatic or vasoconstricting agents, cryotherapy, hot water irrigation, or anterior nasal packing [2]. Bleeding of nose is associated with significant morbidity and rare mortality. Optimal procedure for the epistaxis management would be the one that accomplishes hemostasis with minimal pain, little or no bleeding, and allows the patients to return to their normal daily activities in the shortest period of time.

ABS is a hemostatic agent composed of plant extracts which are *Urtica dioica* (0.06 mg/ml), *Vitis vinifera* (0.08 mg/ml), *Glycyrrhiza glabra* (0.07 mg/ml), *Alpinia officinarum* (0.07 mg/ml), and *Thymus vulgaris* (0.05 mg/ml). Each of the constituents has some effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular

dynamics and cell mediators [3]. The basic mechanism of action for ABS is the formation of an encapsulated protein network representing focal points for vital erythrocyte aggregation. ABS could be used effectively to manage external bleeding in clinical settings such as skin bleeding and/or superficial mucosal blood oozing [4].

This study evaluates the clinical efficacy of ABS in adults undergoing epistaxis management. The aim of this study is to compare the effectiveness of ABS with traditional phenylephrine in patients with anterior epistaxis.

Patients and methods

A total of 49 patients who suffered from anterior epistaxis were included in this study. A prospective, randomized, nonblinded study was undertaken between April 2009 and June 2009. Setting was tertiary referral center. The protocol was approved by the local committee of the ethics for human research. This study was conducted on adult population. Consent form was obtained from the patients in the study.

Patients with anterior epistaxis which was determined by anterior rhinoscopy were included in this study. All of patients had normal full blood count and normal coagulation test values. The following exclusion criteria were used: pregnant, epistaxis after the nasal operation, systemic disease such as hypertension (hypertension was controlled with appropriate medications at the discretion of the emergency department physician before enrollment), posterior epistaxis which was evaluated by endoscopy, risk factors for hemorrhage such as intake of oral anticoagulants or aspirin, patients with abnormal coagulation tests values (International Normalized Ratio (INR) > 4).

Study design

Study design was the use of ABS wet tampon and 0.5% phenylephrine hydrochloride in two different groups. At the start of the epistaxis management, patients were randomly separated in one of the two different groups. 24 of the 49 patients were assigned to the ABS group (group I) and remaining 25 were included in the phenylephrine group (group II).

ABS (Trend Teknoloji Ilac AS, Istanbul, Turkey) is a registered product for direct application, spraying or incorporation in dressing material to injured skin or mucosa. It is a licensed medicinal plant product that provides active hemostasis and is approved in Turkey by the Ministry of Health. ABS is available only in Turkey with a retail cost of $20/ml. We used ABS wet tampon form (2.5 cm × 7 cm/3 ml). The tampon was used only on the bleeding side. The contralateral side was not packed. On the manufacturer's recommendation, the tampon was left in place for 5 min for ABS group of patients treated in this study. If continued bleeding was noted in the ABS group, the ABS tampon was reapplied. After two unsuccessful ABS tampon applications, the patient was crossed over into the phenylephrine group. If the epistaxis still persisted after these procedures, nasal pack was inserted into the nose.

The phenylephrine tampon was used in patients in group II. It was prepared by the staff as 2.5 × 7 cm gauze impregnated with 3 ml 0.5% phenylephrine hydrochloride. Phenylephrine tampon was inserted into the bleeding side for 5 min and then it was taken out from the bleeding nares. The contralateral side was not packed with nasal tampon. The phenylephrine tampon was inserted again if the hemostasis was not achieved. If bleeding still continued after two phenylephrine tampon applications, the patient was crossed over into the ABS group. If the epistaxis still persisted after these procedures, the hemorrhage was controlled by nasal packing.

Data collection and follow up

The staff completed a questionnaire before epistaxis control. They ranked intensity of bleeding as defined by Bergler et al. [5] (1 = stains on napkin, 2 = soaked napkin, 3 = bowl needed).

The number of applications was recorded for the ABS or phenylephrine until hemostasis is reached. If no adverse reaction and bleeding were observed for at least 1 h, the patients were transferred to the home.

Each patient was controlled at day 2 and day 7 after achieving hemostasis. The nasal cavity was examined endoscopically in both the groups. Any continued bleeding was recorded. In addition, physicians recorded any rebleeding during follow-up and the number of epistaxis-related physician visits. Data collected and recorded included demographic parameters, intensity of bleeding, the number of applications of ABS or phenylephrine, frequency of nasal packing, pain experienced during hemostasis, and complications. With the use of a 10-point visual analogue scales (VAS), the patients estimated the pain experienced during hemostasis (0 = no discomfort, 9 = unbearable).

Statistics

Data were entered into SPSS 15 Statistical Software program for analysis. Demographic data were collected and presented as mean ± SD. Student's t test and Mann–Whitney U test were used for means and Chi-square test was used for percentages. 95% Confidence interval, P values less than 0.05 were considered significant.

Table 1 Demographic data of patients in each experimental group. Means ± SD are presented. F: female. Bleeding: intensity of bleeding as defined by Bergler et al. [5]. (1 = stains on napkin, 2 = soaked napkin, 3 = bowl needed). INR: International Normalized Ratio

	Group I	Group II	*P**
n	24	25	
Age (mean ± SD)	40.9 ± 8.5	37.9 ± 9.0	0.24
Percent *F* (%)	54.2	60.0	0.90
Bleeding (mean ± SD)	2.3 ± 0.8	2.1 ± 0.8	0.25
INR (mean ± SD)	1.13 ± 0.19	1.11 ± 0.13	0.87

* *p* values were determined using the Student's *t* test for age, Chi-square test for sex, Mann–Whitney *U* test for bleeding intensity and INR

Table 2 Success rate of ABS and phenylephrine applications

Number of application	Group I (*n*/%)	Group II (*n*/%)	Total (*n*/%)	*P**
1	15 (62.5)	7 (28.0)	22 (44.9)	<0.05
2	4 (16.7)	9 (36.0)	13 (26.5)	<0.05
No	5 (20.8)	9 (36.0)	14 (28.6)	<0.05

Group I ABS group, *Group 2* phenylephrine group

* *p* values were determined using the Chi-square test

Results

Forty-nine patients were included in the study. Table 1 shows the baseline characteristics of the patients after randomization. Age ranged from 20 to 56 years (mean ± SD: 40.9 ± 8.5 years vs. 37.9 ± 9.0, group I vs. group II, $p = 0.24$). There were 54.2% men and 45.8% women in group I and 60.0% men and 40.0% women in group II ($p = 0.90$). There was no statistically significant difference between the two groups concerning these characteristics. Also there was no significant difference between the groups with respect to the intensity of bleeding defined by Bergler et al. [5] (mean ± SD: 2.3 ± 0.8 vs. 2.1 ± 0.8, group I vs. group II, $p = 0.25$). The average INR of patients showed no significant statistical difference between two groups (mean ± SD: 1.13 ± 0.19 vs. 1.11 ± 0.13, group I vs. group II, $p = 0.87$).

62.5% of the patients in group I were successfully treated with only one application and 16.7% were treated with two applications of the ABS tampon. Only 28% of the patients of group II were treated with one application and 36% were treated with two applications of phenylephrine. Therefore hemostasis was achieved for 79.2% of the patients of group I and 64.0% of the patients of group II. These data showed significant difference between two groups with respect to ABS efficacy ($p < 0.05$) (Table 2).

20.8% of ABS patients were crossed over into the phenylephrine group. But hemostasis could not be achieved for these patients by application of phenylephrine also and nasal packing was applied. 36% of phenylephrine group patients were crossed over into the ABS group. Of these patients 44.4% achieved hemostasis by ABS tampon and remaining 55.6% needed nasal tampon.

ABS could not be successful in achieving hemostasis in 35.7% of patients with bleeding intensity of 3, While phenylephrine was not able to stop bleeding in 80% of the patients with bleeding intensity of 3. Also it was observed that ABS successfully treated all bleeding intensity 1 and 2 patients with one application (5 min). On the other hand, phenylephrine was able to stop bleeding with one application in 87.5% of patients with bleeding intensity 1 and in 12.5% of patients with bleeding intensity 2 (Table 3).

Recurrent bleeding was noted in 8.3% of ABS patients, whereas it was observed in 20% of phenylephrine group. This was considered significant ($p < 0.05$).

Patients experienced the same discomfort with insertion of ABS tampon and phenylephrine tampon during achieving hemostasis (mean 10-pt VAS ± SD: 2.75 ± 1.32 vs. 2.36 ± 1.07, ABS vs. phenylephrine, $p = 2.63$).

There were no complications in either experimental group such as blood transfusion, hospitalization, nasal scars, and nasal adhesions.

Discussion

It has been estimated that 60% of the population has had at least one episode of epistaxis throughout their lifetime. Fortunately, only 6% of these people require medical treatment

Table 3 Success rate of ABS and phenylephrine compared against bleeding intensity

Bleeding intensity	Group I A1 (*n*/%)	Group I A2 (*n*/%)	Group I No (*n*/%)	Group II A1 (*n*/%)	Group II A2 (*n*/%)	Group II No (*n*/%)
1	5 (100.0)	0 (0.0)	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)
2	5 (100.0)	0 (0.0)	0 (0.0)	1 (12.5)	6 (75)	1 (12.5)
3	5 (35.7)	4 (28.6)	5 (35.7)	0 (0.0)	2 (20)	8 (80)

Bleeding intensity: 1 = stains on napkin, 2 = soaked napkin, 3 = bowl needed as defined by Bergler et al. [5]. GroupI A1: ABS applied once until hemostasis. Group I A2: ABS applied twice until hemostasis. Group I No: ABS was unsuccessful. Group II A1: Phenylephrine applied once until hemostasis. Group II A2: Phenylephrine applied twice until hemostasis. Group II No: Phenylephrine was unsuccessful

to control epistaxis [6]. Several medical agents such as vasoconstrictors can be used to manage epistaxis. Generally locally applied vasoconstrictors can assist in visualization and control of nasal bleeding. Cocaine has long been used for vasoconstrictive capabilities. Alternatively, oxymetazoline, xylometazolin, and phenylephrine possess remarkable vasoconstrictive abilities [7].

In recent years, other hemostatic agents with different action mechanisms were used effectively for epistaxis also. For example, Surgicele (Johnson and Johnson, Piscataway, NJ) [8] and oxidized regenerated cellulose [9] conform to irregular surfaces and act to stabilize clots during achieving hemostasis. And also Floseal (Baxter Health Care Corp., Deerfield, IL) [10] has been described for use in controlling epistaxis. It is observed that only 65% of epistaxis cases can be controlled by hemostatic agents alone. In our study we used ABS as anterior epistaxis control agent for the first time to our knowledge. It is a unique folkloric medicinal plant extract, which has historically been used in Turkish traditional medicine as a hemostatic agent.

ABS is a novel effective hemostatic agent that has the therapeutic potential to be used in the management of hemorrhage. Blood stopping process is driven based on protein agglutination. ABS stimulates the formation of an encapsulated protein network that provides points for erythrocyte aggregation in the injured vascular area. [3] Furthermore, ABS also interacts with fibrinogen as well as other blood proteins. ABS-induced formation of the protein network affected the entire physiological hemostatic process without affecting any indivudial clotting factor [11]. The levels of coagulation factors II, V, VII, VIII, IX, X, XI, and XIII were not effected by ABS. Therefore, ABS might be used in patients with deficient primary hemostasis and/or secondary hemostasis, including patients with disseminated intravascular coagulation [12].

The data on the efficacy of ABS in gastrointestinal system bleeding are limited to case reports only. In addition, ABS has been used to control upper gastrointestinal bleeding [13], life-threatening arterial bleeding of the digestive tract [14], and bleeding due to solitary rectal ulcer [15]. Bilgili et al. [16]. showed that acute mucosal toxicity, hematotoxicity, hepatotoxicity, nephrotoxicity, and biochemical toxicity were not observed after oral ABS administration in rabbits. They suggested that ABS had no signs of toxicity during their short-term study.

Our study found the success rate of ABS in epistaxis management as 79.2%. We demonstrated that ABS is quicker and more effective than phenylephrine in reaching hemostasis in epistaxis. Fewer ABS patients experienced rebleeding compared to phenylephrine patients during first 7 days after achieving hemostasis. This shows that ABS is a potent agent in anterior epistaxis control. Furthermore 44.4% success rate of ABS on crossed over patients from phenylephrine group made us consider ABS as effective agent to control bleeding in cases that could not be managed by vasoconstrictor agents. Also it was noted that patients treated with ABS experienced the same level of discomfort with phenylephrine.

Demographically, both groups were well-matched with respect to age, sex, bleeding intensity, and INR. The ABS group had the same bleed intensity compared to the phenylephrine group. Our study observed that ABS was of the same efficacy in reaching hemostasis for stains on napkin and soaked napkin hemorrhage, but more effective for bowl needed hemorrhage compared to phenylephrine. More patients were treated by only one application of ABS than phenylephrine. Therefore ABS is quicker alternative to phenylephrine in achieving hemostasis. ABS also proved to be useful in salvaging patients in whom hemostasis was not obtained using phenylephrine. We experienced 36% failure rate of phenylephrine application for anterior epistaxis. ABS was able to control bleeding in nearly two-thirds of the phenylephrine patients who failed application of phenylephrine. On the other hand, 20.8% of ABS patients were crossed over to the phenylephrine group when ABS was not able to stop the bleeding after two attempts. But hemostasis could not be achieved for these patients by phenylephrine also. We found that cases which were not treated successfully by ABS could not be treated by the vasoconstrictor agent.

There were no complications with either procedure, including recurrent bleeding, nasal scars, nasal adhesions, blood transfusion, and hospitalization. We did not observe any adverse reactions after achieving hemostasis for both groups. It is important to emphasize that currently there are no reported side effects after ABS application in the literature possibly due to its natural ingredients [13]–[15]. However, given our small number of patients, this study may have lacked the statistical power to demonstrate this. Also it should be noted that learning curve is not required for ABS, it is a single and easy use, rapid hemostatic agent for epitaxis management.

Conclusion

Our results showed the efficacy of an ABS in adults who suffered from epistaxis. ABS is an effective hemostatic agent of otorhinolaryngologists who are confronted with anterior epistaxis. ABS is effective, safe, quick, and easy alternative to the phenylephrine in patients with anterior epistaxis. Further study could be carried out to determine the possible benefits in the posterior epistaxis.

Conflict of interest statement We do not have a financial relationship with any organization.

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