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The Hemostatic Effect of Ankaferd Blood Stopper in Rat Bleeding Models with Antithrombotic Drug Therapy: An Experimental *In Vivo* Study

Antitrombotik İlaç Tedavisi Uygulanan Sıçan Kanama Modellerinde Ankaferd Kanama Durdurucusunun Hemostatik Etkisi: In Vivo Deneysel Bir Çalışma

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Abstract

Objective: Ankaferd blood stopper is a mixture of five medicinal plant extracts used as a hemostatic agent for management of external hemorrhage. The aim of this study was to evaluate the hemostatic effects of Ankaferd blood stopper (ABS) on bleeding after tooth extraction *in vivo* models with taking antithrombotic drug.

Materials and Methods: Forty-eight male Albino Wistar rats were divided into six groups of 8 animals each. Maxillary right first molar tooth of the rats were extracted under general anesthesia. 2 mL saline solutions were applied topically to Control group (group 1), Warfarin group (group 3) and Heparin group (group 5) on the sockets immediately after extraction. Two ml ABS's were applied topically to Ankaferd group (group 2), Warfarin-Ankaferd group (group 4) and Heparin-Ankaferd group (group 6) likewise. The bleeding time and the amount of bleeding were compared among 6 groups just following the tooth extraction. The collected data results were analysed statistically by the ANOVA followed by Tukey test for pair-wise comparisons.

Results: The bleeding time was longer in Warfarin and Heparin group than the Control group ($p<0.05$), Ankaferd, Warfarin-Ankaferd and Heparin-Ankaferd groups ($p>0.05$). Similiarly, the amount of bleeding of Warfarin group was significantly higher than those of the Control and Warfarin-Ankaferd group ($p<0.05$). The amount of bleeding were lower in Control, Heparin and Heparin-Ankaferd groups but the differences were not statistically significant ($p>0.05$).

Conclusion: Topically administered ABS is less effective on bleeding control of Warfarin-induced bleeding model than Heparin-induced bleeding model in wistar rats. Resulting small difference in between warfarin and heparin should be investigated in future studies.

Öz

Amaç: Ankaferd kanama durdurucu, eksternal hemorajinin tedavisinde hemostatik bir ajan olarak kullanılan beş tıbbi bitki özütünün bir karışımıdır. Bu çalışmanın amacı, Ankaferd kanama durdurucusunun (ABS) antitrombotik ilaç almış *in vivo* modellerde diş çekimi sonrası kanama üzerine hemostatik etkilerini değerlendirmektir.

Gereç ve Yöntemler: Kırk sekiz erkek Albino Wistar sıçan, her biri 8 hayvandan oluşan altı gruba ayrıldı. Sıçanların sağ üst birinci molar dişleri genel anestezi altında çekildi. Ekstraksiyon işleminden hemen sonra soketler üzerinde kontrol (grup 1), Varfarin (grup 3) ve Heparin (grup 5) gruplarına 2 mL salin solüsyonları topikal olarak uygulandı. Ankaferd (grup 2), Warfarin-Ankaferd (grup 4) ve Heparin-Ankaferd (grup 6) gruplarına ise benzer şekilde 2 mL ABS uygulandı. Diş ekstraksiyonunu takiben 6 grupta kanama zamanı ve kanama miktarı karşılaştırıldı. Toplanan veri sonuçları, önce ANOVA ile ardından ikili karşılaştırmalar için Tukey testi ile istatistiksel olarak analiz edildi.

Bulgular: Kanama zamanı, Varfarin ve Heparin grubunda Kontrol grubu ($p<0,05$) ile Ankaferd, Varfarin-Ankaferd ve Heparin-Ankaferd gruplarına göre ($p>0,05$) daha uzun bulundu. Benzer şekilde, Varfarin grubunda kanama miktarı Kontrol ve Varfarin-Ankaferd grubuna göre anlamlı derecede yüksekti ($p<0,05$). Kanama miktarı Kontrol, Heparin ve Heparin-Ankaferd gruplarında daha düşüktü, ancak fark istatistiksel olarak anlamlı değildi ($p>0,05$).

Sonuç: Topikal olarak uygulanan ABS, wistar sıçanlarda, varfarin kaynaklı kanama modelinin kanama kontrolü üzerinde heparin kaynaklı kanama modeline göre daha az etkilidir. Varfarin ve heparin arasında oluşan küçük fark ilerideki çalışmalarda araştırılmalıdır.

Introduction

Bleeding is a common challenging problem especially in patients who take an anticoagulant or antiaggregant treatment (i.e., patients with clotting disorders). Severe bleeding can be a life-threatening condition and should be managed effectively in a variety of ways including mechanic sponge pressing on the bleeding area; vessel ligation; applying chemical or electro-cauterization and cryotherapy; using topical haemostatic or vasoconstrictor agents and etc (1-4). Various haemostatic agents have been investigated for their role in haemostasis for decades (2,4).

As a commonly used blood stopper agent in our country, Ankaferd blood stopper [ABS (Ankaferd Health Products Ltd., İstanbul, Turkey)] is a traditional folk medicinal plant extract that has been approved in the management of cutaneous, dental and postoperative external bleeding. In addition, it has been reported that ABS had bacteriostatic effects on gram positive and gram negative bacterial flora and induced wound healing (3,5-13). Safety, efficacy, sterility and nontoxicity of the product have been shown (http://www.ankaferd.com) (4).

ABS is a unique mixture of five plant extracts (*Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum and Urtica dioica*) (2,3,5,6,10,14). One of the noteworthy studies on this topic has revealed that use of ABS caused the rapid formation of protein network within the serum and plasma (5).

The mechanism of the haemostatic action for ABS is the formation of an encapsulated protein network for vital physiological erythrocyte aggregation. This protein network formation with blood cells, particularly erythrocytes, covers the primary and secondary haemostatic system without independently acting on coagulation factors and platelets (5,6). Other than haemostatic effect, Mihmanli et al. (13) has reported a proliferative effect of ABS on human leukocytes.

In the light of the above-mentioned data, this study aimed to investigate the *in-vivo* haemostatic effect of ABS on warfarin-induced and heparin-induced bleeding model in rats.

Materials and Methods

The study protocol and experimental design were in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC) and were approved by the institutional review board and Animal Ethics Committee of Gaziosmanpaşa University Faculty of Medicine (approval number: 51879863-42).

Ankaferd Blood Stopper®

ABS (Ankaferd Health Products Ltd., İstanbul, Turkey) products are available as a liquid (solution), spray or in a dressing (tampon) forms that contain a standardized mixture of 5 medicinal plant extracts. The liquid form of ABS was used in the study and it includes active ingredients as follows:

0.16 mg of dried leaf of Vitis vinifera, 0.12 mg of dried root of Urtica dioica, 0.14 mg of dried leaf of Alpinia officinarum, 0.18 mg of dried leaf of Glycyrrhiza glabra, and 0.10 mg of dried leaf of *Thymus vulgaris* (1).

Animals

Forty-eight male Wistar rats, with an average weight of 270-320 g, were used in this study. They were housed in specially designed wire cages and maintained on a 12 h-12 h light-dark cycle with a constant room temperature of 23 °C. Rats were

allowed access to water and standard rodent diet ad libitum. All procedure was performed by the same specialist who authorized to animal experiments.

Experimental Design

Because of the limitations of ethics committee on the number of rats, they were not determined by using power analysis. So, 48 male Wistar rats were selected by the directions of Animal Ethics Committee of University and randomly divided into six groups of 8 animals each. The six groups were as follows:

1. Control group (group 1) rats had no pretreatment with any drug.
2. Ankaferd group (group 2) rats had no pretreatment with any drug.
3. Warfarin group (group 3) rats had pretreated with warfarin dissolved in saline (2 mg/kg) orally by a feeding catheter custom-made of silver for 3 consecutive days before experiment.
4. Warfarin-Ankaferd group (group 4) rats had pretreated with warfarin dissolved in saline (2 mg/kg) orally by a feeding catheter custom-made of silver for 3 consecutive days before the experiment.
5. Heparin group (group 5) rats were given an equal volume (0.25 mL) of standard heparin sodium (640 IU/kg) intraperitoneally 3 times a day for 3 consecutive days before the experiment.
6. Heparin-Ankaferd group (group 6) rats were given an equal volume (0.25 mL) of standard heparin sodium (640 IU/kg) intraperitoneally 3 times a day for 3 consecutive days before the experiment.

The maxillary right first molars were extracted under general anaesthesia (Alfamine 10%, Ege-Vet and Rompún®, Bayer HealthCare AG cocktail) using dental instruments (Figure 1). The extraction comprised fiberotomy, luxation, and tooth removal. The surgical wounds were left for secondary healing. Two ml of saline solution was applied to the each empty tooth sockets in group 1, 3 and 5 immediately after the extraction. Two mL of ABS was applied to the extraction sockets in group 2, 4 and 6 (Figure 1) immediately after the extraction.

The animal number in each group was determined according to literature (11,14) knowledge and local ethic committee advice.

Bleeding Time Assay

The bleeding time was measured with a chronometer and the amount of bleeding was measured with a milligram sensitive scale in all 6 groups just started following the tooth extraction. Bleeding time was detected as the time passed after the start of bleeding just following the tooth extraction to cessation of bleeding. Bleeding times were recorded by a single specialist with using a chronometer.

Amount of Bleeding Assay

The amount of bleeding was measured by means of a cotton wool roll. Each cotton roll was weighed before the procedure on a 0.1-g accurate scale by an investigator blinded to the treatment. Immediately after the extraction, cotton roll was inserted to the socket area and when the roll was filled with blood it is removed and weighed again. This process was carried on until the bleeding stopped. The difference in weight was considered as the amount of bleeding.

Statistical Analysis

The collected data results were analysed and also compared among 6 groups statistically by the ANOVA followed by Tukey test for pair-wise comparisons. P values less than 0.05 were considered as statistically significant.

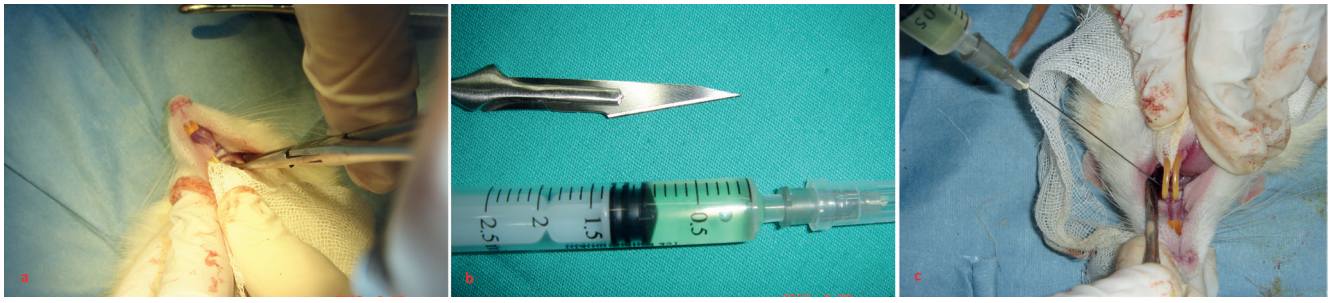

Figure 1. Figure shows the bleeding of rat models which ABS was applied topically; (a) extraction of upper first molar under general anaesthesia using dental instruments, (b) ready-to-use abs solution in dental injector, (c) 2 mL of ABS and saline solutions were applied to the extraction sockets

ABS: Ankaferd blood stopper

Results

There were not any complications observed during the study period and surgical procedure.

Bleeding Time

The mean bleeding time values of all groups were shown in the Table 1. The most prolonged bleeding time was observed in the warfarin group as 47.50 seconds and the shortest bleeding time was observed in Ankaferd Group as 2.87 seconds. Besides, there were not any statistical differences between Ankaferd and Control groups. Regarding the bleeding time, there was no statistically significant difference between warfarin and heparin groups ($p>0.05$). In the Warfarin and Heparin groups, the bleeding time was higher than those of the control and Ankaferd groups and the difference was statistically significant ($p<0.05$). The results showed that ABS administration decreased the bleeding time in both Warfarin-Ankaferd and Heparin-Ankaferd groups, but Ankaferd alone achieved no statistically significant difference when compared with control group (Table 1). The bleeding time of Heparin group was higher than those of the Heparin-Ankaferd, and Warfarin-Ankaferd groups ($p<0.05$).

Although the bleeding time was shortest in the Ankaferd group, there were no statistically significant differences among control, Ankaferd and Heparin-Ankaferd groups ($p>0.05$).

Amount of Bleeding

The amount of bleeding was highest in the Warfarin group as 0.041 grs, and this result was statistically significant when compared with Control and Ankaferd groups ($p<0.05$) (Table 1). There were no statistically significant differences among the Control, Ankaferd, Warfarin-Ankaferd, Heparin and Heparin-Ankaferd groups ($p>0.05$). However, when the results of Warfarin-Ankaferd, Heparin and Heparin-Ankaferd groups were compared with Warfarin group, there were statistically significant differences between them ($p<0.05$).

Warfarin group came first when both bleeding time and amount of bleeding results of all groups were taken into account.

Discussion

Purpose of the present study was to evaluate the haemostatic effect of ABS on warfarin and heparin-induced rat bleeding models. Rat bleeding model is a well-known study model for bleeding control studies. Besides, tooth extraction model was used in order to induce bleeding. Tooth extraction causes bleeding, and bleeding normally stops in a few seconds without intervention in rats. In fact, ABS use in not-drugged rats is not essential for bleeding control but it was necessary to compare the amount and time of the bleeding in this study. Tooth extraction was selected for ABS bleeding models due to frequency of its practice in dental surgery area.

Two distinct anticoagulant drugs were utilized to investigate the haemostatic effects of ABS, warfarin and heparin. It is well-known that these drugs, especially warfarin, cause an enormous bleeding in tooth extraction sockets (15). Warfarin is the most commonly prescribed oral anticoagulant in humans especially who require dental extractions (15,16). Considering dental extractions, patients who take warfarin medication for prevention of cardiovascular thrombosis are at an increased risk of perioperative thromboembolism if the medication is interrupted but there is also a possible increased risk of bleeding

Table 1. The comparison of the bleeding time and the amount of bleeding in between each group

Groups	Control	Ankaferd	Warfarin	Warfarin-Ankaferd	Heparin	Heparin-Ankaferd
Bleeding time (second; sc)	14.87±5.13	2.87±2.10	47.50±13.37[a,b]	18.62±12.59[b,c]	40.50±10.14[a,b,d,e]	9.00±4.40[c]
Amount of bleeding (gram; gr)	0.007±0.005	0.001±0.003	0.041±0.036[a,b]	0.009±0.018[c]	0.015±0.007[c]	00±00[c]

[a]$p<0.05$ differences compared to Control, [b]$p<0.05$ differences compared to Ankaferd, [c]$p<0.05$ differences compared to Warfarin, [d]$p<0.05$ differences compared to Warfarin-Ankaferd, [e]$p<0.05$ differences compared to Heparin

if the medication is continued (15). Heparin has also similar status of its use. It is usually used by parenteral route (16).

The main indication for using anticoagulant therapy such as warfarin, heparin, low molecular weight heparins and etc. is to prevent or manage for arterial and venous thrombosis (7,16). The use of such anticoagulant agents alters the coagulation cascade in the body (1,16). One of the most important factors in coagulation is the vitamin K. Warfarin is one of the most common used vitamin K antagonist agent and it is quickly adsorbed and well tolerated by oral route. The anticoagulant effect of warfarin is slowly established but has a relatively prolonged effect, through a half-life of at least 48 hours (14,16). Heparin has some different effects on the coagulation but also activates anti-thrombin and other proteases involved in the blood clotting system that causes coagulation problems (1). The results of the present study showed that warfarin and heparin, as anticoagulant drugs, caused an important increase on bleeding time. ABS administration normalized the increase and stopped the bleeding as well. According to results of study, these anticoagulant drugs also increased the amount of the bleeding.

According to previous studies, oral surgical and clinical approach to the patients who take anticoagulant medication made it necessary to stop the anticoagulant treatment for several days or reduce the dose of anticoagulant drug for preventing severe life-threatening hemorrhage (7). But, currently, this radical approach for the treatment of patients undergoing anticoagulant therapy were replaced to an approach that advises to perform the oral surgical procedures without any intervention of anticoagulant treatment but with attention on the local bleeding control methods (7). Therefore, ABS was used as a local haemostatic agent to control warfarin and heparin-induced bleeding in present study. As a result, bleeding control was achieved by using ABS in rats which have been receiving either of these anticoagulant drugs or not.

Ankaferd blood stopper is a unique standardized herbal mixture being used as a haemostatic agent in Turkey for many years. The exact mechanism of ABS is yet unknown but there is a growing body of evidence on the efficacy of ABS on homeostasis (1,3-5,7,8,10-12,14). Additionally, it was found that ABS shortened the bleeding time in the rats receiving and not receiving anti-coagulant therapy both. Meric Teker et al. (17) reported that ABS-induced formation of the protein network affected the physiological haemostatic process without affecting any individual clotting factor. The present study also supports this literature knowledge.

Similar to the present results, Cipil et al. (14) reported that the bleeding time was reduced to 44% with ABS use in animals pretreated with warfarin. Sacco et al. (16) also demonstrated that ABS had a haemostatic effect on the cut tails of rats alone or in the presence of heparin or aspirin medication. Iynen et al. (1) showed that ABS irrigation effectively prevented nasal bleeding in rats pretreated with heparin sodium. Meric Teker et al. (17) reported the ABS as an effective, safe, quick, and easy-to-use alternative to the phenylephrine in patients with anterior epistaxis. But, they also revealed secondary haemorrhage in a few patients with using ABS. Iynen et al. (1) reported that ABS successfully shortened the haemostasis time and decreased the bleeding volume.

Warfarin and heparin have different biochemical anti-haemostatic actions on coagulation cascade mentioned in the literature (1,16). In contrast, the previous results have some contradictions. ABS does not affect the entire blood clotting system including coagulations factors (7,14,18-21). But, heparin and warfarin affect entire clotting system with various different ways (14). ABS has a different level of action on both anti-haemostatic agents.

The present study revealed that ABS more effective on heparin experiment models than warfarin without statistically significance. In addition the previous result of the present study, ABS should be used on warfarin models as a local haemostatic agent due to statistically significance between Warfarin group, Control group, and Warfarin-Ankaferd group in terms of bleeding time and amounts ($p<0.05$). Similarly, these previous results valid on heparin including groups ($p<0.05$).

Study Limitations

The present study had a limitation as international normalization ratio (INR) test was not used for standardization of anti-coagulation level of blood. According to the literature, Clinicians should attempt to identify contributing factors for prolonged non-

therapeutic INR. So, the risk of coagulation can be minimized, as well as costs of hospital stay and laboratory exams can be reduced (22). It is important to achieve the therapeutic levels of INR in the patients treated by anticoagulants (23).

Conclusion

The results of the present study concluded that topically administered ABS to empty tooth sockets immediately after the extraction is effective for homeostasis in warfarin and heparin-induced bleeding in rats. But, efficiency of ABS over warfarin-induced and heparin-induced bleeding patterns and whether if it affects in the same way or not, should be investigated in further studies. Also, the exact mechanism of ABS over haemostasis and the necessity of this agent in clinic use should be investigated in the future studies.

Ethics

Ethics Committee Approval: Animal Ethics Committee of Gaziosmanpaşa University Faculty of Medicine (approval number: 51879863-42).

Informed Consent: It was not taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., İ.A., M.K.T., Concept: N.A., İ.A., Design: N.A., C.A., Data Collection or Processing: N.A., H.E., M.K.T., C.A., Analysis or Interpretation: N.A., H.E., Literature Search: N.A., İ.A., H.E., Writing: N.A., H.E.

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