EXPERIMENTAL STUDY

Effects of Algan Hemostatic Agent on bleeding time in a rat tail hemorrhage model

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ABSTRACT

BACKGROUND: Algan Hemostatic Agent (AHA) is a multi-herbal extract containing a standardized amount of Achillea millefolium, Juglans regia, Lycopodium clavatum, Rubus caesius or Rubis fruciosus, Viscum album, and Vitis vinifera, each of which is effective in hemostasis. In this study, we aimed to investigate the effects of AHA on bleeding time in a rat tail hemorrhage model.

METHODS: Forty-eight Sprague Dawley rats (5–7 weeks old, 180–210 g) were randomly and equally allocated to six groups as follows: heparin plus saline (heparinized control), heparin plus AHA-soaked sponge, heparin plus liquid form of AHA, saline (non-heparinized control), AHA-soaked sponge and liquid form of AHA. Heparin (640 IU/kg) was administered intraperitoneally three times a day for three days in heparinized groups. For the bleeding model, the tail of rats was transected. According to the study group, either saline- or AHA-soaked sponge or liquid form of AHA was applied over the hemorrhage area. In AHA- or saline-soaked sponge groups, once the bleeding time had started, it was checked every 10 seconds. If the bleeding did not stop after 40 seconds, it was accepted as a failure. In liquid AHA group, the duration of bleeding was measured using a chronometer and defined as the time (seconds) from wounding until the bleeding stopped.

RESULTS: Bleeding time in the heparinized and non-heparinized control groups was over 40 seconds. After applying the sponge form of AHA on the wound area, bleeding time was significantly shortened to less than 20 seconds in both heparinized and non-heparinized rats ($p<0.001$ for both). The liquid form of AHA stopped bleeding in 5.0±1.2 seconds and 8.0±1.3 seconds in heparinized and non-heparinized groups, respectively.

CONCLUSION: AHA is a highly effective topical hemostatic agent in a rat tail hemorrhage model, thus may provide for a unique clinically effective option for control of bleeding during surgical operations or other emergencies.

Keywords: Algan Hemostatic Agent; bleeding time; hemorrhage; hemostasis; rat.

INTRODUCTION

Immediate control of bleeding during surgical operations or other emergencies is crucial to avoid negative outcomes of blood loss.[1] Therefore, exogenous hemostatic agents are needed to control the minor or major bleedings from traumatic lacerations, ruptures, fractures, or surgeries.[2] Sever-

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al hemostatic products have been shown to be effective in bleeding control.[3–6] These products have different forms, such as powders, liquid, gels, and sheets, according to the area used. While powder and gel forms are preferred to be used on irregular surface areas, sheet-type hemostatic agents are preferred in cases where pressure can be applied in the region.[1]

Collagen, oxidized cellulose, and chitosan are currently widely used as hemostatic agents.[3–7] However, during the use of these products, some problems, such as the increased risk of infectious diseases and low pH-induced inflammation, are frequently encountered.[8–12] Thus, there is no consensus on which of these agents has the best hemostatic efficacy and safety profile. As a result, none of the topical hemostatic agents has become dominant over the others, and the search for a more effective and safe topical hemostatic agent continues.

Algan Hemostatic Agent (AHA) is a multi-herbal extract containing a standardized amount of *Achillea millefolium, Juglans regia, Lycopodium clavatum, Rubus caesius or Rubis fruciosus, Viscum album, and Vitis vinifera*, each of which is effective in hemostasis (Patent No: TR2015 0018 A2). AHA exerts a topical hemostatic effect by forming a thick polymeric network which traps blood and blood components passively, and gives rise to a mechanical barrier in the bleeding zone. Its hemostatic efficacy and safety have been shown in various experimental bleeding models.[13–16] Additionally, it has the advantages of low cost and no special storage requirements. However, there is still a need for further preclinical efficacy and safety studies on experimental animal models before proceeding with clinical trials.

Rat tail hemorrhage model is one of the most commonly used animal models for preclinical efficacy studies of hemostatic agents.[17–19] In this study, we aimed to evaluate the effects of two different forms of AHA (sponge and liquid) on bleeding time in a rat tail hemorrhage model.

MATERIALS AND METHODS

Animals and Experimental Design

Forty-eight Sprague Dawley rats (5–7 weeks old, 180–210 g) were used for this study. Animals fed ad libitum and kept under standard laboratory conditions according to 12-hour dark-light period. The rats were randomly and equally divided into isx groups each containing eight rats: 1) heparin plus saline-soaked sponge (heparinized control), 2) heparin plus AHA-soaked sponge, 3) heparin plus liquid form of AHA, 4) saline-soaked sponge (non-heparinized control), 5) AHA-soaked sponge and 6) liquid form of AHA. Heparin (640 IU/kg) was administered intraperitoneally three times a day for three days in three heparinized groups. The same amount of saline was administered to three non-heparinized groups.

This study was approved by the Institutional Animal Experiments Local Ethics Committee of Kırıkkale University (number, 2018/09) and conformed with the 2015 reprint of the Public Health Service Policy on Humane Care and Use of Laboratory Animals Policy on Humane Care and Use of Laboratory Animals.

Surgical Procedure

Rat tail hemorrhage model was created as described previously in the literature.[19] All rats were anesthetized using ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (10 mg/kg) intramuscularly. After cleaning the rats' tails with batticon, 4-cm proximal part of the tail was excised using a guillotine (Fig. 1).

Once the bleeding started, the area was compressed for 10 seconds with a saline (Fig. 1) or 2 cc AHA-soaked sponge (Fig. 2). In the study groups treated with liquid form of AHA,

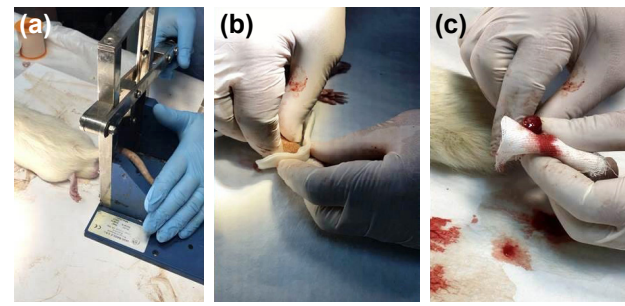

Figure 1. In control group, 4-cm proximal part of the rat's tail was excised using a guillotine under general anesthesia, **(a)**. Once the bleeding started, the area was compressed for 10 seconds with a saline-soaked sponge **(b)**. Bleeding continued for 420 sec and 280 sec after administration of saline-soaked sponge in heparinized and non-heparinized rats, respectively **(c)**.

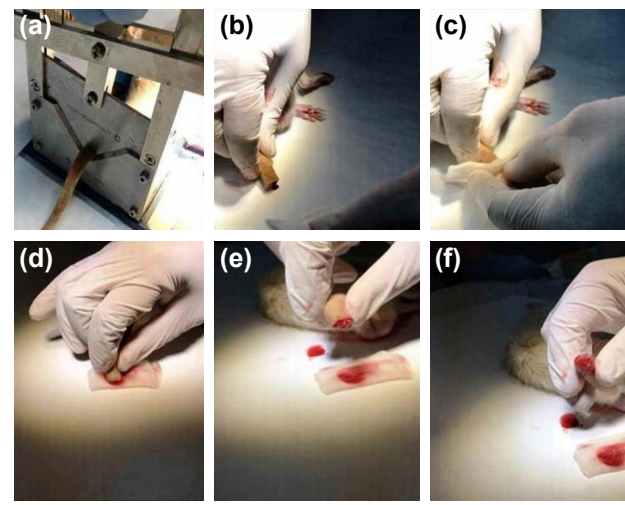

Figure 2. In AHA-soaked sponge group, 4-cm proximal part of the rat's tail was excised using a guillotine under general anesthesia **(a)**. Once the bleeding started **(b)**, the area was compressed for 10 seconds with a 2 cc AHA-soaked sponge **(c)**. Bleeding stopped within 20 seconds after the administration of AHA-soaked sponge **(d-f)**.

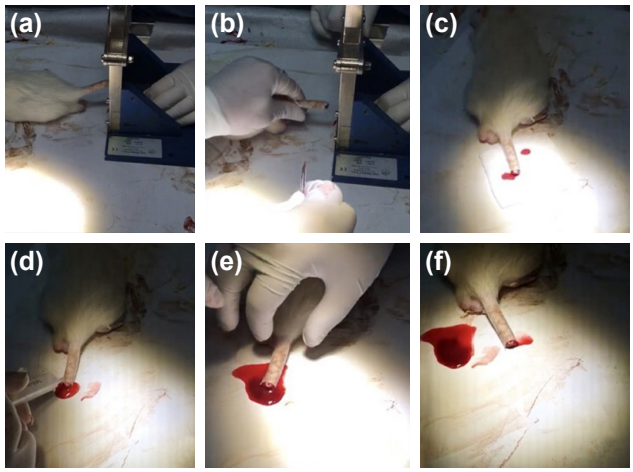

Figure 3. In liquid AHA group, 4-cm proximal part of the rat's tail was excised using a guillotine under general anesthesia **(a, b)**. Once the bleeding started **(c)**, the area was applied with liquid form of AHA without compression **(d)**. Bleeding stopped within 10 seconds after the administration of liquid form of AHA **(e, f)**.

no pressure was applied to the bleeding region and it was left open (Fig. 3).

Bleeding Time

The bleeding time was measured as decribed previously.[20] In AHA- or saline-soaked sponge groups, once the bleeding time started, it was checked every 10 seconds. If the bleeding did not stop after 40 seconds, it was accepted as a failure. In liquid AHA group, the duration of bleeding was measured using a chronometer and defined as the time from wounding until the bleeding stopped. At the end of this study, the rats were euthanized with 100 mg/kg intravenous sodium thiopental (Pental Sodyum®, İ.E. Ulagay, İstanbul, Turkey).

Statistical Analysis

This study data were given as number, percentage, mean, and standard deviation. Spearman rank test was used for the comparison of control and AHA-soaked sponge groups in terms of bleeding time category. Due to the difference in bleeding time measurements, liquid AHA and AHA-soaked sponge groups could not be compared.

The Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The results were assessed at a 95% confidence interval, and a p-value below 0.05 was assumed to indicate the statistical significance.

RESULTS

While the bleeding from the wound area was continuing in heparinized and non-heparinized saline-soaked sponge group (control) after 40 sec, bleeding stopped within 20 sec in all rats treated with AHA-soaked sponge group (Figs. 1 and 2, Table 1). In heparinized rats, AHA-soaked sponge stopped bleeding within 10 sec in two out of eight rats (25%) and within 20 sec in the remaining six rats (75%) (Fig. 2, Table 1). However, in non-heparinized rats of AHA-soaked sponge group, bleeding stopped within 10 sec in half of the rats (n=4) and within 20 sec in other half of the rats (n=4) (Fig. 2, Table 1). After the application of the sponge on the wound area, bleeding time significantly shortened in both heparinized and non-heparinized rats ($p<0.001$, Table 1).

AHA liquid form stopped bleeding in 8.0±1.3 sec (range 6–10 sec) and 5.0±1.2 sec (range 3–7 sec) in heparinized and non-heparinized groups, respectively (Fig. 3, Table 2). Although liquid AHA and AHA-soaked sponge groups could not be compared statistically, it is possible to say that liquid form of AHA is more effective in bleeding control. Liquid form of AHA controlled bleeding in both heparinized and non-heparinized rats in less than 10 sec, AHA-soaked sponge controlled bleeding in 20 sec in all rats (Fig. 4).

Table 2. The mean bleeding time in liquid AHA group

Bleeding time	Liquid form of AHA (n=16)
Heparinized (n=8)	8.0±1.3 sec (range 6–10 sec)
Non-heparinized (n=8)	5.0±1.2 sec (range 3–7 sec)

Data are presented as mean±standard deviation (range). Time to bleeding was measured with a chrometer in liquid AHA group. AHA: Algan Hemostatic Agent.

Table 1. The number of rats in the saline- or AHA-soaked sponge groups according to when bleeding stopped

	Bleeding time	Saline-soaked sponge (Control) (n=16)	AHA-soaked sponge (n=16)	p
Heparinized	<10 sec	–	2	<0.001
	<20 sec	–	6	
	>40 sec	8		
Non-heparinized	<10 sec	–	4	<0.001
	<20 sec	–	4	
	>40 sec	8		

Bleeding was controlled every 10 seconds in both saline- and AHA-soaked sponge groups. AHA: Algan Hemostatic Agent.

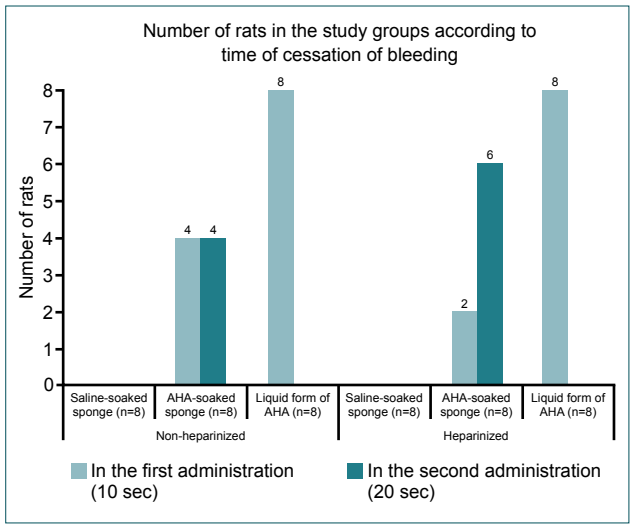

Figure 4. The number of rats in the study groups according to when bleeding stopped. AHA liquid form stopped bleeding in under 10 seconds in all rats of both heparinized and non-heparinized groups. AHA-soaked sponge stopped bleeding after the first administration in four rats of non-heparined group and in two rats of heparinized group.

DISCUSSION

In this study, hemostatic effects of liquid and sponge forms of AHA were evaluated on an experimental rat tail hemorrhage model, and both were effective on bleeding, significantly shortening bleeding time in both heparinized and non-heparinized rats compared to saline control groups. Both liquid and sponge form of AHA stopped the bleeding in under 10-20 seconds in the rat tail hemorrhage model.

Various materials and chemicals have been evaluated for their hemostatic efficacy in the literature.[21–24] However, there is no consensus on which hemostatic agent is more effective. While some studies found collagen to be a more effective hemostatic agent, others reported that chitin-containing substances were more effective.[21–24] Mean bleeding time of different hemostatics, such as polyurethane, collagen, oxidized regenerated cellulose, gelatin, chitosan added polyurethane, varies between 21 and 28 seconds.[21–24] In the present study, bleeding time after AHA hemostasis was under 10 and 20 seconds in liquid and sponge forms, respectively.

In the literature, the bleeding time in healthy Sprague Dawley rats range between 5 and 7 minutes.[19] In one study, bleeding time was 35 seconds after gauze application and 54 seconds in rats without gauze application.[17] Sogut et al.[19] reported that bleeding stoped at 3.29 minutes in heparined rats, and at 1.57 minutes in non-heparinized rats. In consistent with these previous studies, we found that bleeding time was over 40 seconds in non-heparinized and heparinized control groups, respectively. For measurement of bleeding time, we used the rat tail hemorrhage model, a widely accepted experimental model for bleeding studies.[25–27]

Some plants have traditionally been used as bleeding stoppers. The mechanism underlying the bleeding-stopping effect of these plants is the astrengenic effect of predominantly tannin type complex polyphenolic phytochemicals.[28] These plants have been shown to shorten the coagulation time and increase the coagulation of platelets in the area of bleeding.[13–16,28]

AHA is a newly developed multi-herbal extract containing six hemostatic plants.[13–16] In previous animal studies, AHA has been shown to effectively stop bleeding without any acute, subacute or chronic side effects on tissues.[13–16] Despite these previous studies, it is still necessary to further evaluate the effects of AHA on bleeding before proceding to clinical studies. AHA has been suggested to stop bleeding by physical mechanisms.[13–16] When AHA is applied to the hemorrhage area, it becomes a gel and forms a barrier by surrounding the polymers, blood and blood components in the environment. When AHA used in a moist environment, it quickly polymerizes into a thin elastic film that has high tensile strength and firmly adheres to the tissue on which it is applied.

In the present study, AHA liquid form was applied directly onto the bleeding area without any compression. However, AHA-soaked sponge was applied to the bleeding area with a compression for 10 seconds. AHA liquid and sponge forms contain the same amount of AHA. Although compression has a suppressive effect on compression, AHA liquid form was more effective in stopping bleeding than sponge form. The reason for higher efficacy of the liquid form in providing hemostasis may be the deterioration of the hemostasis provided by AHA-soaked sponge during the removal of the sponge. In comparison to the products used for hemostasis in the literature, AHA controlled the bleeding in shorter time in the rat tail hemorrhage model.[17,19,25–27] Given differences in designs and outcomes of studies, such as weight of animals, experience of intestigators, technical equipment, and blood vessel variations, it is clear that comparative studies are needed to demonstrate the superiority of AHA over other plant-based products. Therefore, the main limitation of the study is lack of an active control to compare the hemostatic effectiveness of AHA. Additionally, this study evaluated only the acute effects of AHA. Its chronic effects and safety profile needs to be assessed in further studies. Despite its limitations, the present study is important in terms of demonstrating the hemostatic efficacy of AHA, an easy to apply herbal product, on an accepted experimental model.

Conclusion

AHA, a standardized multi-herbal extract, is a highly effective topical hemostatic agent in a rat tail hemorrhage model. AHA may provide for a unique clinically effective option for control of bleeding during surgical operations or other emergencies. Based on the findings of the present experimental study, further comparative clinical studies are needed to confirm its safety and effectiveness on humans.

Ethics Committee Approval: Approved by the local ethics committee.

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Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZET*

Algan hemostatik ajan'ın sıçan kuyruk kanama modelinde kanama zamanı üzerine etkisi

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AMAÇ: Algan hemostatik ajan (AHA), hemostatik etkinliği bilinen *Achillea millefolium, Juglans regia, Lycopodium clavatum, Rubus caesius* ya da *Rubis fruciosus, Viscum album* ve *Vitis viniferea*'yı standardize miktarda içeren bir bitki ekstresidir. Bu çalışmada AHA'nın sıçan kuyruk kanama modelinde kanama zamanı üzerine etkinliğinin değerlendirilmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Kırk sekiz Sprague Dawley sıçan (5–7 haftalık, 180–210 g), altı çalışma grubuna rastgele ve eşit sayıda randomize edildi. Çalışma grupları şunlardır: Heparin + salin (heparinize kontrol), heparin + AHA ile ıslatılmış sünger, heparin + sıvı AHA, salin (heparinize olmayan kontrol), AHA ile ıslatılmış sünger, sıvı AHA. Heparinize gruptaki sıçanlara üç gün boyunca günde üç kez intraperitoneal heparin (640 IU/kg) uygulandı. Kanama modeli oluşturmak için sıçanların kuyrukları kesildi. Çalışma grubuna göre kanama bölgesine salin ile ıslatılmış sünger, AHA ile ıslatılmış sünger ya da sıvı AHA uygulandı. Salin ya da AHA ile ıslatılmış sünger uygulanan gruplarda, kanamanın durumu her 10 saniyede bir kontrol edildi. Kanama 40 saniye sonra hala durmamış ise uygulanan tedavi başarısız kabul edildi. Sıvı AHA uygulanan grupta, kanama süresi kuyruk kesilmesinden kanama durana kadar geçen süre olarak tanımlandı ve kronometre ile ölçüldü.

BULGULAR: Heparin uygulanan ve uygulanmayan kontrol gruplarında kanama süresi 40 saniyenin üzerinde kaydedildi. Kanama bölgesine AHA ile ıslatılmış sünger uygulanan heparinize olan ve olmayan sıçanlarda ise kanama süresi anlamlı olarak kısalarak 20 saniyenin altına düştü (her iki grup için de $p<0.001$). Sıvı AHA uygulanan heparinize olan ve olmayan sıçanlarda kanama süresi sırasıyla 5.0±1.2 saniye ve 8.0±1.3 saniye olarak ölçüldü.

TARTIŞMA: AHA, sıçan kuyruk kanama msodelinde yüksek etkinliğe sahip bir hemostatik ajandır. Cerrahi girişimlerde ve acil durumlarda kanama kontrolü sağlanması için kullanılabilecek bir tedavi seçeneği olarak değerlendirilebilir.

Anahtar sözcükler: Algan Hemostatik Ajan; hemostaz; kanama; kanama zamanı; sıçan.

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