Journal of Applied Biological Sciences
E-ISSN: 2146-0108 16(3): 386-395, 2022
DOI: 10.5281/zenodo.7113975
Research Article

INVESTIGATION OF THE CLINICAL EFFICACY OF DIFFERENT FORMS OF ALGAN HEMOSTATIC AGENT (AHA) IN THE RAT ABDOMINAL AORTIC BLEEDING MODEL

Ali Kumandas[1*], Husamettin Ekici [2]

[1] *Kırıkkale University, Faculty of Veterinary Medicine, Department of Surgery, Kırıkkale, Turkiye*
[2] *Kırıkkale University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Kırıkkale, Turkiye*

**Corresponding Author:*
E-mail: alikumandas@kku.edu.tr

(Received 15th June 2022; accepted 17th July 2022)

ABSTRACT. In cases of death due to trauma, failure to control bleeding is shown as one of the main reasons. Therefore, effective and rapid control of bleeding is very important in reducing traumatic death rates. Many hemostatic products are used for this purpose. Algan Hemostatic Agent (AHA) is a herbal hemostatic agent obtained from a mixture of different plants. The aim of this study was to determine the efficacy of the herbal extract Algan Hemostatic Agent (AHA) in different pharmacological forms in the abdominal aortic injury model of rats. Sixty four 5-8 weeks old male rats were randomly divided into 8 groups, each consisting of eight rats (4 groups were heparinized and 4 groups were non-heparinized). Experimental abdominal aortic hemorrhage was established and physiological saline soaked sponge was applied to the control group. AHA liquid soaked sponge, liquid and powder forms were applied to the experimental groups. Bleeding time was found to be significantly shorter in other AHA groups compared to the control group. The AHA powder form was able to control bleeding by 62.5% and 87.5% in the heparinized and non-heparinized groups, respectively, in the second application (3 minutes). In the second application, the AHA sponge formulation was able to control bleeding at 37.5% and 62.5% in the heparinized and non-heparinized groups, respectively. In the second application, the AHA liquid formulation was able to control the bleeding by 50% and 75% in the heparinized and non-heparinized groups, respectively. After three applications, bleeding was controlled in all AHA groups. Bleeding could not be controlled in the heparinized and non-heparinized control groups and the bleeding time was over 6 minutes. According to the results of this study, it has been shown that AHA is an effective hemostatic agent in bleeding control compared to the control group. Again, this study showed that the technique of creating an injury with a needle in the aortic hemorrhage model is more standardized than other methods.

Keywords: *Algan hemostatic agent (AHA), aort, bleeding, rat.*

INTRODUCTION

Major vascular injuries and uncontrolled hemorrhages are reported to be important problems constituting approximately 40% of post-traumatic trauma deaths. It is one of the leading causes of potentially preventable death in trauma patients in both human and veterinary medicine. It is known that most hemorrhagic deaths in severe trauma occur within the first 6 hours after the trauma. Therefore, effective and rapid control of bleeding is very important in reducing traumatic death rates. In trauma patients, direct pressure is first applied to the bleeding site to stop the circulation as quickly as possible [1]. Effective and rapid control of bleeding is very important in reducing mortality rates. There are many medical products for this purpose and they are reported to be used. Some of the locally

available hemostatic products in the market are; microporous polysaccharide fibrin glues, poly-N-acetylglucosamine, microporous hydrogel-forming polyacrylamide, linear polymer, oxidized cellulose, etc. [2, 3, 4, 5, 6, 7, 8, 9].

Despite the great advances in medicine, an ideal product that can be used in the control of serious bleeding has not yet been produced. For this, there is a need to produce faster and more effective hemostatic products.

Algan Hemostatic Agent (AHA) is a herbal extract obtained from a standardized mixture using different parts of six different plants. Each of the plants that make up AHA has a content that is effective in hemostasis. All necessary biocompatibility tests such as sensitization, cytotoxicity, irritation, and hemodynamic tests of AHA have been performed in previous studies, and these results have confirmed the safety and effectiveness of in vivo use as a hemostatic agent [10]. It can be easily applied locally and does not require special storage conditions.

This study was conducted to investigate the hemostatic effect of different pharmacological forms of AHA in the abdominal aortic hemorrhage model in rats.

MATERIALS AND METHODS

In this study, 64 male wistar albino (WA) rats were used to demonstrate the efficiency following the application of 3 different forms AHA (AHA liquid, AHA liquid soaked sponge, and AHA powder forms) (Algan Group Health Services Import and Export Industry and Trade Limited Company, Istanbul, Turkey) on the abdominal aorta. This study was approved by the Institutional Animal Experiments Local Ethics Committee of Kirikkale University (Decision Number, 2018/11).

Study design

The experimental procedure was performed as described in a previous study [11, 12]. In the study, 64 male rats which are 210-255 g, 5-7 weeks old were used. Rats were fed ad libitum and examined under standard laboratory conditions according to the 12-hour dark-light period. Rats were first randomly divided into two heparinized and non-heparinized groups. Then, each of these groups was divided into 4 groups of 8 randomly selected (Table 1). A dose of 640 IU/kg heparin (Nevparin® 25,000IU/5ml, Mustafa Nevzat Pharmaceutical Company, Gayrettepe, Istanbul, Turkey) was administered intraperitoneally to heparinized group three times a day for 3 days. The other group was given the same amount of isotonic saline.

Table 1. *Experiment groups*

Groups	Definition of the groups
Group 1	Heparinized control group
Group 2	Heparinized AHA powder group
Group 3	Heparinized AHA liquid group
Group 4	Heparinized AHA liquid soaked sponge group
Group 5	Non-Heparinized control group
Group 6	Non-Heparinized AHA powder group
Group 7	Non-Heparinized AHA liquid group
Group 8	Non-Heparinize AHA liquid soaked sponge group

Surgical procedure

The experiment was conducted under general anesthesia. All rats were anesthetized with 100 mg/kg ketamine hydrochloride (Ketasol 10%®, Richter pharma ag, Wels, Austria) and 10 mg/kg xylazine hydrochloride (XYLAZINBIO 2%®, Bioveta, a.s., Czech Republic), intramuscularly. The abdominal regions of the rats were shaved and wiped with povidone-iodine. The abdominal aorta was reached by a sterile midline abdominal incision approach. The abdominal aorta proximal to the iliac bifurcation was injured with a 21 gauge needle tip. 2 mL of AHA liquid, AHA powder, and AHA soaked gauze was applied to the bleeding site in the experiment groups and 2 mL physiological saline-soaked gauze was applied in the control group. The AHA products sterilized by gamma sterilization in the study were used.

Bleeding Test

The duration of bleeding was evaluated according to the protocol in the literature [12]. When the abdominal aorta has been damaged and bleeding has begun, another person has compressed the bleeding area for 10 seconds with a dry sponge, then the sponge has been lifted off. AHA dust was applied directly to the bleeding area, and AHA and the saline-soaked sponge were placed in this area, and pressure was applied on them. Bleeding was checked 1 minute after the time started. If bleeding stopped, it was recorded as the bleeding stopped at 1 minute. In the first minute, if the bleeding did not stop, the same amount of material was applied and continued to compress for up to 2 minutes. Two minutes later the bleeding was checked and if the bleeding stopped, it was recorded as the bleeding stopped at the second application (3 minutes), if the bleeding did not stop, the same procedure was applied for the third time and was waited for 3 minutes. An additional 3 minutes later, the bleeding was checked and recorded as stopped bleeding at the third application (6 minutes). If the bleeding was still continuing after the third application, recorded as failed. The rats were euthanized with CO_2 at the earliest 10 minutes after the end of the experiment.

Statistical analysis

Animal weight, bleeding time, and compliance scores were calculated, and mean values were compared between groups using analysis of variance (ANOVA). When differences were found, the difference group was determined by Duncan's multiple range test. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$. SPSS software version 20.0 (SPSS Inc., Chicago, IL) was used to analyze the study data. Excel 2010 was used for all the computations regarding the intraobserver precision.

RESULTS AND DISCUSSION

There was no difference between groups in terms of the mean weight of the rats. The bleeding time was significantly shorter in all AHA groups compared to the control group ($p<0.01$) (Table 2). Any of the AHA forms couldn't control bleeding in the first application. The product in AHA powder form was able to control bleeding by 62.5% and 87.5% in the heparinized and non-heparinized groups, respectively, in the second application (3 minutes) (Figure 1). The product in AHA sponge form was able to control the bleeding in heparinized and non-heparinized groups in the second application at

37.5% and 62.5% respectively (Figure 2). The product in AHA liquid form was able to control the bleeding in heparinized and non-heparinized groups in the second application of 50% and 75% respectively (Figure 3). After three applications, bleeding was controlled in all AHA groups. The bleeding in heparinized and non-heparinized control groups couldn't be under control, and the time was over 6 minutes (unsuccessful). In the control group animals, hemorrhagic shock findings were detected because the bleeding could not be controlled after abdominal aorta bleeding (Table 2). After the bleeding was controlled in all AHA groups, the bleeding site was cleaned with isotonic saline and controlled. There wasn't seen new bleeding in this area. AHA powder form was found to be more effective than the control group, AHA sponge form, and liquid form. Although the AHA powder form controlled bleeding more effectively than other AHA forms, no statistically significant difference was observed. However, a statistically significant difference was found when compared with the control group.

Table 2. *Homeostasis time of the control and AHA groups*

		[1]First application (1 minute)	**[2]Second application (2 minutes)**	**[3]Third application (3 minutes)**	**[4]Unsuccessful (>6 minutes)**	**p**
Heparinized	Control	0 (0%)	0 (0%)	0 (0%)	8 (100%)	p<0.01
	AHA Powder	0 (0%)	5 (62.5%)	3 (37.5%)	0 (0%)	
	AHA Sponge	0 (0%)	3 (37.5%)	5 (62.5%)	0 (0%)	
	AHA Liquid	0 (0%)	4 (50%)	4 (50%)	0 (0%)	
Non-heparinized	Control	0 (0%)	0 (0%)	0 (0%)	8 (100%)	p<0.01
	AHA-Powder	0 (0%)	7 (87.5%)	1 (12.5%)	0 (0%)	
	AHA Sponge	0 (0%)	5 (62.5%)	3 (37.5%)	0 (0%)	
	AHA Liquid	0 (0%)	6 (75%)	2 (25%)	0 (0%)	

[1] Number of rats whose bleeding was controlled in first application, [2] Number of rats whose bleeding was controlled in the second application, [3] Number of rats whose bleeding was controlled in the third application, [4] Number of rats whose bleeding was not controlled in third application.

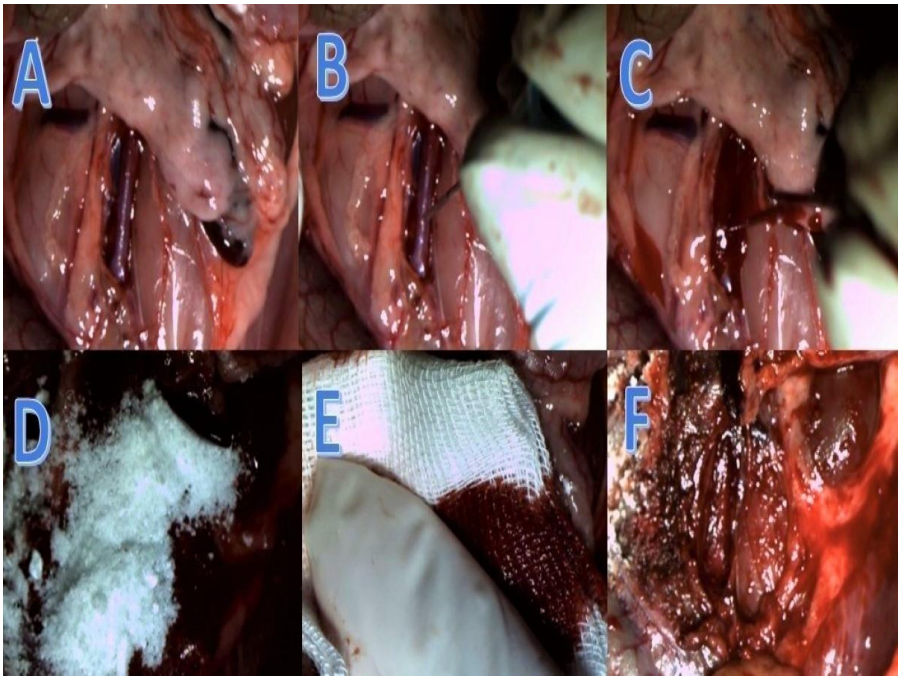

Fig. 1. *AHA powder form application. A: Abdominal aorta. B: Damage of the abdominal aorta with syringe needle. C: Bleeding. D: AHA powder application. E: Light press application on the area with sponge for 2 minutes. F: Bleeding appears to be under control after removal of the sponge.*

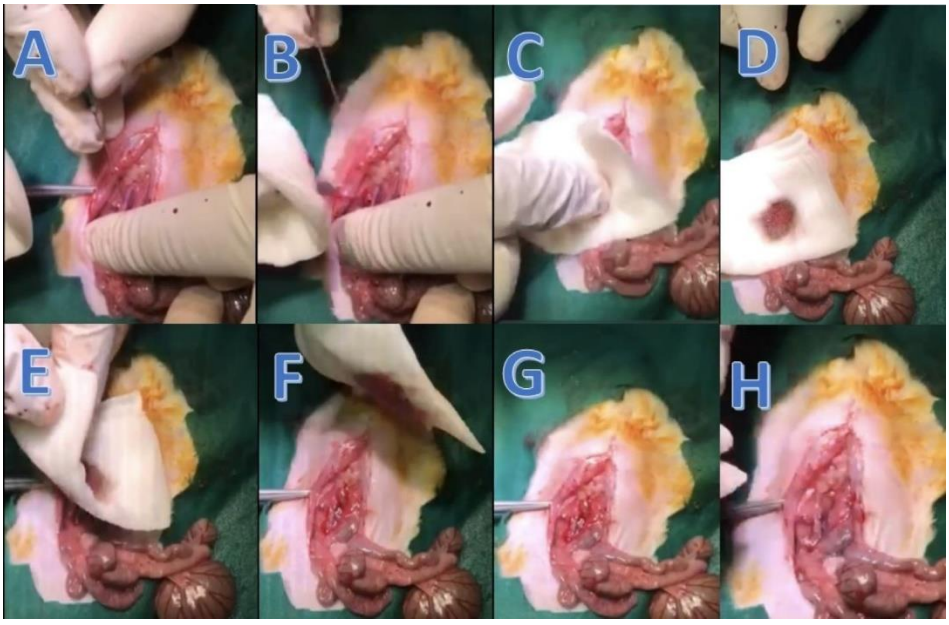

Fig. 2. *A: AHA sponge form application. Damage of the abdominal aorta with the syringe needle. B: Bleeding. C, D: Light press application with AHA impregnated sponge for 2 minutes. E, F: Lifting the sponge. G: Bleeding appears to be controlled after sponge is removed. H: Bleeding does not start despite waiting.*

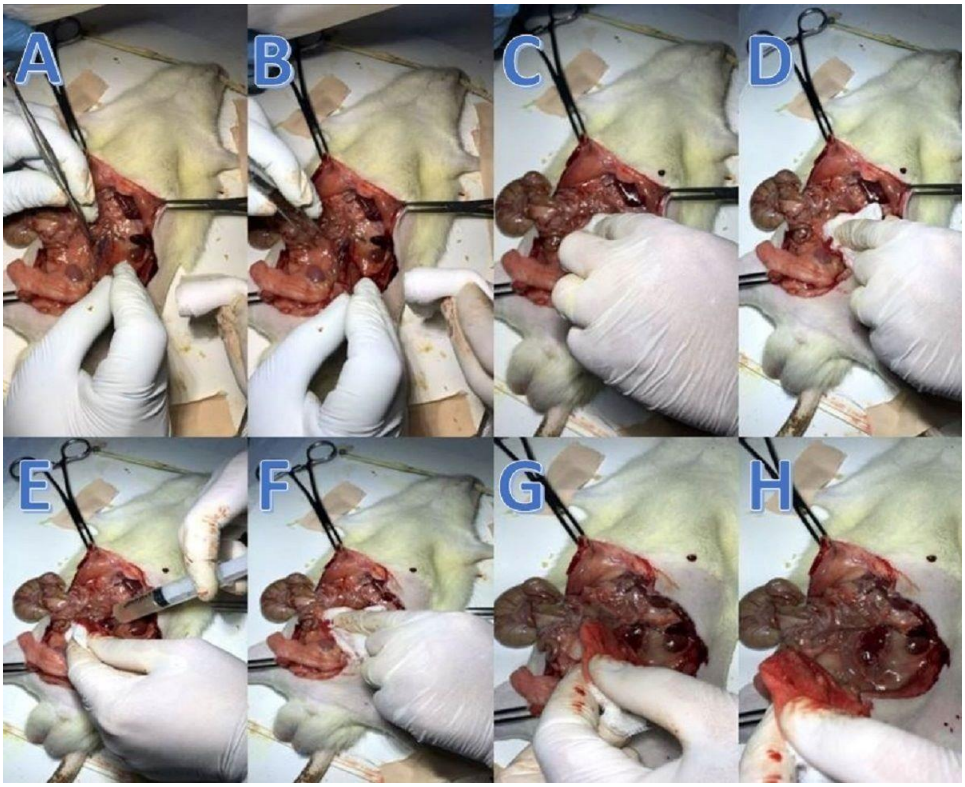

Fig. 3. *AHA liquid form application. A: Damage of the abdominal aorta with the syringe needle. B: Bleeding. C, D: Pressure application with dry sponge on bleeding area for 10 seconds. E: AHA Liquid form application. F: Light press application with sponge for 2 minutes. G, H: Appearance of bleeding control after removal of the sponge.*

Studies on achieving hemostasis in a short time continue today. Getting the bleeding under control as soon as possible is very important both for saving the lives of trauma patients and for surgical patients to have a successful operation. Various studies are carried out to examine the effects of hemostatic agents and to increase their effectiveness [2-5]. In some studies, it has been reported that the mean duration of abdominal aortic bleeding in the control group varies. It is reported that due to many factors such as animal weight, practitioner experience, technical variability, vessel variability, laboratory conditions, etc., it is necessary to compare known hemostatic agents with other new products to evaluate the hemostatic activity [8, 9, 11, 12, 13]. In contrast to the incision technique described by Onk et al.2016 [13], in this study, it was aimed that the needle puncture technique would be a standard cut of the aortic injury. The study data showed that standard bleeding was possible in this technique (Figure 1a).

Various hemostatic products have been developed to be used in bleedings of different shapes [14, 15, 16, 17, 18]. The properties expected to be found in the products produced for this purpose can be listed as follows; fast and high activity, minimal tissue reactivity, no antigenic reaction, low cost, easy absorption. In addition, an ideal hemostatic agent should be easy to use, require minimal training, be effective in both arterial and venous bleeding, be non-toxic, and non-anaphylactic. Currently, no hemostatic agent has all of these properties. There are various products in the market that contain different synthetic

and natural source materials to provide hemostasis when necessary [19, 20, 21, 22, 23, 24].

Caustic agents coagulate the proteins, leading to tissue necrosis and providing hemostasis by increasing the thickening of the wound by increasing the formation of clots. Non-caustic agents are hemostatic agents that physically and physiologically demonstrate their effects. Physical agents play an active role in increasing the formation of hemostasis, bringing platelet aggregation and a physical blanket that facilitates coagulation. Such agents include porcine gelatin, microporous polysaccharide beads, hydrophilic polymers in the form of potassium salt, oxidized-regenerated cellulose and microfibrils. However, due to the risk that such agents can lead to granulomatous foreign substance reaction, it is warned to avoid use in infected areas and near the eyes [2]. Porcine gelatin creates a mechanical barrier in the bleeding area. However, it may swell causing damage to tissues and nerves around the hemorrhagic area. Microporous polysaccharide Spheres are bio-inert particles prepared from starch. It is suitable for small cuts. It can be effective within 5 minutes. Because the body can be absorbed in 24-48 hours, surgery is used. Oxidized-regenerated cellulose products, made from vegetable cellulose, also create physical barriers to capping, venous, and small arterial bleeds [2, 4]. Absorbed in the body in 7-14 days. Microfibrillar collagen is prepared from purified cattle collagen. Platelets cluster on the collagen surface. Before use, the wound should be dried with the help of a sponge and the product should be applied directly onto the wound with a special applicator. This is a disadvantage. Hemostasis occurs between 1 and 5 minutes. Factor concentrators are agents with high absorbing power, such as zeolites (inert volcanic minerals), rapidly absorb the water in the hemorrhagic region, ensuring that cellular and protein components rapidly clot. However, due to the exothermic reaction, it is no longer preferred. Mucoadhesive agents strongly adhere to the tissues and physically cover the bleeding wounds. In this type of product, chitosan is obtained by deacetylation of chitin, a polysaccharide obtained from shellfish. When the chitosan comes into contact with anionic erythrocytes, the chitosan immediately forms a cross-link and sticks strongly to the wound surface. It is thought that this process does not interfere with platelet or clotting factors. Procoagulant supports are another group of hemostatic agents that aims to have rapid effects of procoagulant factors in the bleeding area. Aluminosilicate accelerates the natural coagulation reactions of nanoparticles and kaolin, a white substance. Kaolin initiates coagulation by converting factor XII into its active form when it comes into contact with blood. Activated factor XII activates factor XI and its precursor. This coagulation reaction is initiated. These group products, which are generally marketed in powder form, can be easily applied directly onto the wound. However, most of them are ineffective in wounds caused by weapons that cause deep puncture wounds such as bullets, knives, and sharps tools. The hemostatic agent used in this study was prepared in different forms to be used in bleeding types that may occur as a result of different types of injuries.

Alginate-based wound dressing, one of the herbal hemostatics stated to be used as a hemostatic in some studies, is the substance of the polysaccharide structure obtained from algae. It forms a protective layer as a coating material. While it can be useful in bleeding without excessive blood loss, it is ineffective in pressure bleeding. Traditionally, some herbs are known to be used as astringents. The mechanism of action of these herbs on hemostasis is mainly based on the astringent property of complex polyphenolic phytochemicals [8, 9]. However, some herbs have been reported to shorten the clotting

time and increase the clotting of platelets, reducing the risk of infection and inflammation [10, 11].

The plants that make up the AHA are yarrow, walnut, club moss, blackberry, European mistletoe and vine. There are numerous publications in the literature showing these plants have a hemostatic effect [13, 14, 15, 16, 17]. When preclinical studies are examined, it is seen that the hemostasis mechanism of AHA is physical. It was determined that when AHA was applied to the bleeding site, it became a gel and formed a barrier by surrounding fibrin, blood, and blood components in the environment. AHA has a structure that polymerizes quickly when used in a humid environment. At the same time, it forms a thin elastic film with high tensile strength and adheres tightly to the tissue to which it is applied. According to the data obtained, AHA shows its hemostatic effect by forming polymeric networks where it is applied. AHA creates a physical barrier at the bleeding site by passively trapping blood and blood components in the reticular structure [24, 25, 26, 27, 28].

CONCLUSION

Various techniques, such as scalpel and scissors, have been reported to create wounds in the aortic bleeding model. Although these techniques are suitable for large animals, the needle puncture technique for rats standardizes the experimental conditions in terms of creating a standard hole. This study showed that the technique of creating injury with the needle in the aortic bleeding model is more standardized than other methods.

AHA's advantages over other readily available products include efficacy and ease of application. Evaluation of only the acute phase effects of AHA resulted in limited data from this study. It is thought that more comprehensive studies are needed for this situation. AHA is a new agent and preclinical studies have been completed. In animal experiments, it has been shown that there is no acute, subacute, or chronic harmful effect on the tissues (unpublished data). Despite all these studies, it is necessary to study the effects of the medium and long term in the veins and tissues.

According to the results obtained from this study, although AHA produces a very good hemostatic effect, the real difference between other hemostatic agents used for this purpose in the abdominal aortic bleeding model can only be demonstrated by comparative studies. It is thought that this situation will be revealed in future comprehensive studies.

Conflict of Interest. The authors declared that there is no conflict of interest.

Authorship Contributions. Concept: A.K., H.E. Design: A.K., H.E. Data Collection or Processing: A.K., H.E. Analysis or Interpretation: A.K., H.E. Literature Search: A.K., H.E. Writing: A.K., H.E.

Financial Disclosure. This study supported by The Algan Group Health Services (Algan Group Health Services Import and Export Industry and Trade Limited Company, Istanbul, Turkey). The company had been role of the study materials provided for scientists, but had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

[1] Brunett, PH., Cameron, PA. (2012): Trauma in adults. In: Tintinalli, JE., Stapczynski, JS., Ma, OJ., Cline, DM., Cydulka, RK., Meckler, GD. (eds). Tintinalli's Emergency Medicine: A Comprehensive Study Guide. 17th ed. New York, USA, McGraw Hill.

[2] Hanks, JB., Kjaergard, HK., Hollingsbee, DA. (2003): A comparison of the haemostatic effect of Vivostat patient-derived fibrin sealant with oxidised cellulose (Surgicel) in multiple surgical procedures. Eur Surg Res 35: 439-444.

[3] Ersoy, G., Kaynak, MF., Yilmaz, O., Rodoplu, U., Maltepe, F., Gokmen, N. (2007): Hemostatic effects of microporous polysaccharide hemosphere in a rat model with severe femoral artery bleeding. Adv Therapy 24: 485-492.

[4] Ward, KR., Tiba, MH., Holbert, WH., Blocher, CR., Draucker, GT., Proffitt, EK., Bowlin, GL., Ivatury RR., Diegelmann, RF. (2007): Comparison of a new hemostatic agent to current combat hemostatic agents in a swine model of lethal extremity arterial hemorrhage. J Trauma 63: 276-283.

[5] Beyazit, Y., Kurt, M., Kekilli, M., Goker, H., Haznedaroglu, IC. (2010): Evaluation of hemostatic effects of Ankaferd as an alternative medicine. Altern Med Rev 15: 329-336.

[6] Burkatovskaya, M., Tegos, GP., Swietlik, E., Demidova, TN., Castano, PA., Hamblin, MR. (2006): Use of chitosan bandage to prevent fatal infections developing from highly contaminated wounds in mice. Biomaterials 27: 4157-64.

[7] Aktop, S., Emekli-Alturfan, E., Ozer, C., Gonul, O., Garip, H., Yarat, A., Goker, K. (2014): Effects of Ankaferd Blood Stopper and Celox on the tissue factor activities of warfarin-treated rats. Clin Appl Thromb Hemost 20: 16-21.

[8] Ucar, Albayrak, C., Caliskan, U., Haznedaroglu, IC., Goker, H. (2008): Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper. J Int Med Res 36: 1447-1448.

[9] Kose, R., Sogut, O., Demir, T., Koruk, I. (2012): Hemostatic efficacy of folkloric medicinal plant extract in a rat skin bleeding model. Dermatol Surg 38(5): 760-6.

[10] Midi, A., Kumandas, A., Ekici, H., Bayraktar, F., Karapirli, K., Karahan, S., Turk, M., Ozyurek, HE. (2019): Investigation of the Efficacy of Algan Hemostatic Agent in Liver Laceration Model in Rats. EJMO 3(1): 37–42.

[11] Abacioglu, S., Aydin, K., Buyukcam, F., Kaya, U., Isik, B., Karakilic, ME. (2016): Comparison of the Efficiencies of Buffers Containing Ankaferd and Chitosan on Hemostasis in an Experimental Rat Model with Femoral Artery Bleeding. Turk J Haematol 33(1): 48-52.

[12] Kandemir, O., Buyukates, M., Kandemir, NO., Aktunc, E., Gul, AE., Gul, S., Turan, SA. (2010): Demonstration of the histopathological and immunohistochemical effects of a novel hemostatic agent, Ankaferd Blood Stopper, on vascular tissue in a rat aortic bleeding model. J Cardiothorac Surg 5(1): 110-16.

[13] Onk, OA., Aksut, M., Ozcelik, F., Onk, D., Sertoglu, E., Erol, HS., Karaman, U., Tuncer, ON., Yiginer, O., Erkut, B.(2016): Haemostatic Effects of Topical Ankaferd Blood Stopper® On Bleeding Time in A Rat Abdominal Aortic Bleeding Model. Kosuyolu Heart J 19(2): 103-107.

[14] Yesilada, E., Sezik, E., Honda, G., Takaishi, Y., Takeda, Y., Tanaka, T. (1999): Traditional medicine in Turkey IX. Folk medicine in north-west Anatolia. J Ethnopharmacol 64(3): 195-210.

[15] Hsieh, CL., Lin, CH., Wang, HE., Peng, CC., Peng, RY. (2015): Gallic Acid Exhibits Risks of Inducing Muscular Hemorrhagic Liposis and Cerebral Hemorrhage—Its Action Mechanism and Preventive Strategy. Phytother Res 29(2): 267-280.

[16] Yao, C., Hao, R., Pan, S., & Wang, Y. (2012): Functional foods based on traditional Chinese medicine. In Bouayed J, ed. Nutrition Well-Being and Health Chapter 8; InTech. Europa, pp. 179-200.

[17] Quamar, MF., Bera, SK. (2014): Ethno-medico-botanical studies of plant resources of Hoshangabad district, Madhya Pradesh, India: retrospect and prospects. J Plant Sci Res 1(1): 1-11.
[18] Goker, H., Haznedaroglu, IC., Ercetin, S., Kirazli, S., Akman, U., Ozturk, Y., Firat, HC. (2008): Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper®. Int J Med Res 36(1): 163-170.
[19] Colman, RW., Marder, VJ., Clowes, AW., George, JN., Goldhaber, SZ. (2005): Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 5th ed., Lippincott, Williams&Wilkins, Philadelphia, pp.1-16.
[20] Glick, JB., Kaur, RR., Siegel, D. (2013): Achieving hemostasis in dermatology Part- II. Topical hemostatic agents. Indian Dermatol Online J 4(3): 172-6.
[21] Jackson, MR. (2001): New and potential uses of fibrin sealants as an adjunct to surgical hemostasis. Am J Surg 18: 36-39.
[22] Chapman, WC. (2001): Costasis Multi-center Collaborative Writing Committee. A novel collagen-based composite offers effective hemostasis for multiple surgical indications: Results of a randomized controlled trial. Surgery 129: 445-450.
[23] Waibel, KH., Haney, B., Moore, M., Whisman, B., Gomez, R. (2011): Safety of chitosan bandages in shellfish allergic patients. Mil Med 176(10): 1153-6.
[24] Schwartz, M., Madariaga, J., Hirose, R., Shaver, TR., Sher, L., Chari, R., Colonna, JO., Heaton, N., Mirza, D., Adams, R., Rees, M., Lloyd, D. (2004): Comparison of a new fibrin sealant with standard topical hemostatic agents. Arch Surg 139: 1148-1154.
[25] Midi, A., Kumandaş, A., Ekici, H., Arda, S., Karahan, S., Şimşek, AK., Yesilada, E. (2018): Investigation of the effectiveness of algan hemostatic agent in renal venous bleeding model in rats. EJMI 2: 129-32.
[26] Midi, A., Ekici, H., Kumandas, A., Durmus, O., Bodic, B., Tiryaki, M., Balik, MS., Yesilada, E. (2019): Investigation of the effectiveness of algan hemostatic agent in bleeding control using an experimental partial splenectomy model in rats. Marmara Med J 32(1): 27-32.
[27] Midi, A., Ozyurek, HE., Karahan, S., Ekici, H., Kumandas, A., Turkmen, I., Kocabas, E., Turk, M., Demirel, OU., Yesilada, E. (2018): Investigation of efficacy of the plant based algan hemostatic agent in hepatectomy bleeding model in rats. EJMI 2: 195-201.
[28] Ekici, H., Kumandas, A., Ozbaykus, AC., Dizdaroglu, H., Midi, A., Balik, MS., Yesilada E. (2022): Investigation of The Effectiveness of Plant Based Algan Hemostatic Agent in a Rat Model of Femoral Arterial Bleeding. Bezmialem Sci 10(1): 88-96.