Research Article / Araştırma Makalesi

Hemostatic Efficacy of Algan Hemostatic Agent in Renal Vein Incision Model in Rats

Algan Hemostatik Ajan'ın Sıçan Renal Ven İnsizyon Modelinde Hemostatik Etkinliği

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Abstract

Background: The aim of this study is to evaluate the acute hemostatic effects of liquid and powder forms of AHA in severe bleeding model of rat renal vein.
Materials and Methods: 10-12 weeks old, 24 male Wistar albino rats were randomly divided into three groups of eight animals each as the control, AHA liquid, AHA powder. The left renal artery and vein were revealed with a 3 cm vertical incision and the tip of the injector was used to puncture renal vein, causing bleeding. In all animals, regular gauze patch was pressed over the incised area for 10 seconds as soon as the bleeding began. Immediately after removing the sponge; physiological saline, AHA liquid and powder were applied with compress to injured site of relevant groups for 2 minutes, respectively. The time was recorded by chronometer and the area was checked after two minutes. Hemostasis that was not achieved after three applications was accepted as failure.
Results: Cessation of the bleeding failed in all rats after three successive 2-minute physiological saline impregnated gauze applications in control group. Among AHA-treated groups, significant hemostasis efficacy was obtained from the liquid form than that of powder. Within first two minutes, bleeding in renal veins of five rats was controlled successfully in liquid group whereas powder group achieved hemostatic success in four rats.
Conclusions: The vessel incision model in our study revealed fast-acting physical hemostatic properties of the liquid and powder formulations of AHA in the renal vein. This natural applicable product could be used to induce hemostasis in rat models of bleeding caused by various renal damages or trauma, and it could also prevent local bleeding in humans. More studies are needed to compare the efficacy of different formulations of the polysaccharide-based herbal product in various organs and surgical models.

Key Words: Hemostasis, Kidney, Renal Vein, Algan Hemostatic Agent, Bleeding, Rat

Öz

Amaç: Bu çalışmanın amacı, sıçan renal veni şiddetli kanama modelinde sıvı ve toz AHA formlarının akut hemostatik etkilerini değerlendirmektir.
Materyal ve Metod: 10-12 haftalık, 24 erkek Wistar albino sıçan kontrol, AHA sıvı ve AHA toz olarak her biri sekiz hayvan içeren üç gruba rastgele ayrıldı. Sol renal arter ve ven 3 cm'lik vertikal insizyon ile ortaya çıkarıldı. Renal venin kesi yaralanması için enjektör ucu kullanıldı ve kanama oluşturuldu. Kanama başladığında tüm hayvanlarda insize edilen alan üzerine 10 saniye süresince gazlı bez ile bası uygulandı. Ardından, serum fizyolojik, AHA sıvı ve toz ilgili gruplarda kesi bölgelerine sırasıyla iki dakika süreyle uygulandı. Süre kronometre ile kaydedildi ve kanama alanı iki dakika sonra kontrol edildi. Üç uygulama sonrasında hemostaz sağlanamadıysa, başarısız olarak kabul edildi.
Bulgular: Kontrol grubundaki tüm sıçanlarda ardışık 2 dakikalık serum fizyolojik emdirilmiş gazlı bez uygulamalarında kanama durdurulması başarısız oldu. AHA uygulanan gruplarda, sıvı formdan toza göre daha önemli hemostaz etkinliği sağlandı. İlk iki dakika içinde, sıvı grubunda beş sıçanın böbrek damarlarındaki kanama kontrol edilirken, toz grubunda dört sıçanda hemostatik başarı elde edildi.
Sonuç: Çalışmamızdaki damar kesi modeli, AHA' nın sıvı ve toz formülasyonlarının renal vende hızlı etkili fiziksel hemostatik özelliklerini ortaya çıkarmıştır. Doğal bir ürün olan AHA, çeşitli böbrek hasarları ya da sıçanda travmaya bağlı kanama modellerinde hemostaz sağlamak için kullanılabilir ve ayrıca insanlarda lokal kanamayı önleyebilir. Polisakkarit bazlı bitkisel ürünün farklı formülasyonlarının çeşitli organlarda ve cerrahi modellerde etkinliğini karşılaştırmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Hemostaz, Böbrek, Renal Ven, Algan Hemostatik Ajan, Kanama, Sıçan

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Introduction

Severe vascular injuries constitute a major part of preventable deaths when uncontrolled, and coagulopathy-induced multiple organ failure is observed in one third of trauma patients (1). Hemorrhage-related deaths mostly occur within the first six hours after trauma (2). There are variety of techniques in order to control continuous bleeding such as the use of tourniquets, hemostatic suturing and compression (3). In addition, maintaining hemostasis during surgical operations is crucial, since the hemorrhage might cause complications or necessitate transfusion (4). Awaiting the natural hemostatic mechanism to happen is impossible at the time of an operation, which makes the use of additive methods to obtain hemostasis necessary (5). Therefore, there is an increasing need for fast-acting and efficient hemostatic products. Most important characteristics of an ideal hemostatic agent are providing sustainable hemostasis, leaving no residues subsequently to biodegradation, indicating good biocompatibility, ease of production and low market price (6). Chitosan linear polymer (Celox®), poly-N-acetylglucosamine and oxidized cellulose (Bloodcare®), microporous hydrogel-forming polyacrylamide (BioHemostat®), n-acetyl glucosamine polymer (Chitin®), ankaferd blood stopper® (ABS), fibrin glue and microporous polysaccharide hemosphere (TraumaDEX®) are some examples of currently accessible hemostatic products (7-13). The different functions of hemostatic agents in obtaining hemostasis are inducing the fibrin formation, inhibiting the fibrinolysis or covering the bleeding site not permitting any leakage (14).

The Algan Hemostatic Agent (AHA) is a herbal extract containing a standardized mixture of Achillea millefolium, Juglans regia, Lycopodium clavatum, Rubus caesius or Rubis fruciosus, Viscum album, and Vitis vinifera with no additives (Patent application publication no. TR2015 0018 A2) (15). All of the plants that are components of AHA have hemostatic characteristics both separately and in combination (16). In terms of mechanism of action, AHA rapidly polymerizes to form a thin, elastic film with a significant tensile strength and strongly adheres to moist tissue (17). Variable tests have been performed in order to measure the biocompatibility of AHA. The outcomes of the tests measuring cytotoxic effects, sensitization, hemodynamic mechanism, irritability effects and the previous studies on the efficacy of the AHA confirmed that AHA is a safe and competent hemostatic agent (18-20). Additionally, it has a reasonable cost and it is convenient in terms of local application and storage. The aim of this study is to evaluate the acute hemostatic effects of liquid and lyophilized powder forms of inexpensive, simple to use Algan Hemostatic Agent in severe bleeding model of rat renal vein.

Materials and Methods

Animals

Adult 10-12 weeks old, 24 male Wistar albino rats weighing between 250-280 g were used in this research. The rats were kept in an air-conditioned animal room in standard sterile, clean, polypropylene cages under standard vivarium conditions with 12 h light/dark cycles, 22±3°C room temperature and 55%±5% humidity. All animals were fed with a standard rat chow and water provided as *ad libitum*. All experiments were performed after one week-long of adaptation period. Animal experiments were carried out in compliance with the ethical standards approved by the Local Animal Experiments Ethics Committee of Marmara University Istanbul, Turkey (Ethics Committee Approval No:11.2021mar, Dated:11.01.2021).

Experimental design, surgical procedure and bleeding test

Animals were randomly divided into three groups of eight animals each and the groups were randomly designated as the control (physiological saline solution impregnated gauze), AHA liquid group and AHA powder group. Since the powder form was obtained by lyophilization, it was also referred to as lyophilized powder. The surgical procedure used in this study was performed in accordance with the literature and under anesthesia (16). Physiological saline (2ml) and AHA liquid form (2ml) were soaked in gauze patches before operation. Powder form was ready to use and directly applied. All animals were intraperitoneally sedated with 100 mg/kg ketamine hydrochloride (Ketalar, Eczacıbaşı, Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Rompun, Bayer, Istanbul, Turkey). Skin or finger nipping response, palpebra or corneal reflex, pulse rate, respiration rate, and other physiological indicators were used to monitor anesthetic depth. The left abdominal area of the rats were wiped, shaved and disinfected with 10% povidone-iodine solution, followed by layers of the skin and subcutaneous tissues were cut open with 3 cm vertical incision, revealing the left renal artery and vein through hilar vascular dissection. The tip of the injector was used to puncture the left renal vein, causing bleeding. In all rats, a regular gauze patch was pressed over the incised area for 10 seconds as soon as the bleeding began. Immediately after removing the sponge, physiological saline solution impregnated gauze was applied with compress to the injured site of control group for two minutes. Aha liquid impregnated gauze was also applied with compress to the injured area of AHA liquid group for two minutes and AHA powder was imposed on injured site with compress for two minutes. Chronometer was started to record the time and the area was checked after two minutes by veterinary surgeon, histologist and medical students. If there was no bleeding, the first 2-minutes of applications were recorded as “successful”. If the bleeding did not cease after 2 minutes, the procedure was repeated with the same material amounts and the hemorrhage was monitored again. If the bleeding had ceased, the application was recorded as "second 2-minutes successful," but if there was still bleeding, the procedure was repeated for the third time. If the bleeding had ceased with the third application, it was recorded as “third 2-minutes successful”. Hemostasis that

was not achieved after the third application in each group was recorded as “failed". All animals were euthanized by decapitation under deep anesthesia at least 10 minutes later the hemostasis.

Statistical Analysis

The Pearson Chi squared test and Fisher exact test (if necessary) were used to analyze categorical variables. Demographic information were summarized using frequency distribution (n and %). A two-tailed p < 0,05 was considered significant for all tests. The data of this study was analyzed by Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL).

Results

In the control group, the cessation of the bleeding failed in all rats after three 2-minute physiological saline solution impregnated gauze applications and this was statistically significant (p=0,001) (Table 1). The first 2-minutes of bleeding control application success rates for the AHA liquid and powder were 62.5% and 50%, respectively. Moreover, when the first 2-minute application success rates of the liquid and powder forms of AHA were compared, the success rates of the liquid were significantly higher than that of the powder (Table 1). The second 2-minutes of bleeding control application success rates for the AHA liquid and powder were 100% and significantly higher than the control group second 2-minutes of bleeding control application (p=0,003) (Table 1). When the success rates of application results were higher than the first 2-minute application outcomes and both formulations were more effective than the physiological saline solution applied control group (Table 1). AHA liquid and powder were compared, second 2-minute.

Table 1. Evaluation of bleeding test results in study groups

	Application Results			
	Positive	**Negative**	**Total**	**p**
1st Application (2 minutes)				
AHA liquid group	5 (62,5)	3 (37,5)	8 (100)	0,026
AHA powder group	4 (50)	4 (50)	8 (100)	
Control group	0 (0)	8 (100)	8 (100)	
Total	9 (37,5)	15 (62,5)	24 (100)	
2nd Application (2 minutes)				
AHA liquid group	3 (100)	0 (0)	3 (100)	0,002
AHA powder group	3 (100)	1 (0)	4 (100)	
Control group	0 (0)	8 (100)	8 (100)	
Total	6 (40)	9 (60)	15 (100)	
3rd Application (2 minutes)				
AHA liquid group	0 (0)	0 (0)	0 (0)	na
AHA powder group	1 (100)	0 (0)	1 (100)	
Control group	0 (0)	8 (100)	8 (100)	
Total	0 (0)	8 (100)	8 (100)	
Result				
AHA liquid group	8 (100)	0 (0)	8 (100)	0,001
AHA powder group	8 (100)	0 (0)	8 (100)	
Control group	0 (0)	8 (100)	8 (100)	
Total	16 (66,7)	8 (33,3)	24 (100)	

AHA: Algan Hemostatic Agent, n (%), na: non available

Discussion

Kidney injuries and the resulting bleeding are considered as vital, since the kidney is one of the most vascular structures in the body besides being responsible for important functions (21). Hemostatic agents enable the operators to control any hemorrhage quickly during a surgical procedure, thereby lowering the risk of complications. AHA is a promising instrument in treating acute hemorrhage and is a natural herbal product with standardized plant mixture. All of the AHA-forming plants alone have effects on endothelial cells, blood cells, angiogenesis, vascular dynamics and mediators that may contribute to hemostatic effects and wound healing (22-27).

In this study, AHA was tested for its hemostatic property on renal vein incision model, since it is crucial to keep kidney’s vascular structures intact in case of any injury. AHA achieved hemostasis on sites of bleeding of various sizes and locations by polymerizing into a high tensile strength film that adheres tightly to the tissue. According to a study conducted on porcine kidneys four hemostatic agents, none of which was a plant-based hemostat, were applied directly into the collecting system of kidneys and the application resulted in obstruction that needed over five days to resolve (28). Given the fact that the testing of the product cannot be performed on humans, rats were elected for this study, as the renal veins of rats are quite prominent with the ease of accessibility. Lyophilized powder and liquid forms of AHA were studied and both forms were found to

be highly effective in the management of hemorrhage in renal venous bleeding model. Until the bleeding area could be treated, application of the same amount of AHA solution was repeated and compressed in every two minutes. In the control group, rats were treated with tampon solution and the application was repeated in every two minutes. The better hemostasis efficacy was detected in the AHA-treated experimental groups than in the control group. Among the experimental groups, the significant hemostasis efficacy was obtained from the liquid form of AHA. The success rates in the first application of AHA liquid form are significantly higher than that of the AHA powder form. A previous study that focused on the hemostatic effects of gel, powder and liquid forms of AHA on renal bleeding revealed the shortest bleeding duration was achieved by use of powder form, followed by gel and liquid in contrast to our study (16). Experimental group treated with the liquid form of AHA, the bleeding of the renal veins of five rats were controlled successfully within 2 minutes (62.5% success rate). After the second application of AHA, the bleeding of remaining rats were treated, and the success rate was reached to 100% within 4 minutes suggesting that the physical properties of liquid form obtained fast hemorrage control in this study. Kheirabadi et al. reported that a fibrin sealant foam reduced the parenchymal hemorrhage in anticoagulant-treated rats at success rates of 56% and 66% when compared to the untreated and placebo treated groups, respectively (29). Lyophilized powder form of AHA achieved 50% success in controlling hemorrhage in 2 minutes. The success rate was 100% after the subsequent application. Humphreys et al. had similar results in terms of mean durations of bleeding until the hemostasis was achieved for the polysaccharide hemosphere-treated renal injury models on pigs (30). In another study, partial nephrectomy was performed on rats and after the renal artery and vein being occluded with a clamp for hilar control, three different hemostatic agents were applied, each of which achieved hemostasis on the resected site within less than one minute (31). Furthermore, patients who had undergone partial nephrectomy were reported to exposed with a tissue sealant that achieved hemostasis within one to two minutes on the moist resected sites (32).

In total, the time until the complete hemostasis was achieved did not surpassed six minutes for any of the injury sites in both experimental groups treated with AHA. Nine rats were treated within two minutes, six rats within four minutes and one rat within six minutes. Another study investigating the hemostatic effect of microporous polysaccharide hemospheres on pigs that undergone partial nephrectomy reported the mean hemostasis time as 4,67 minutes for the experimental groups (33). A study comparing two different hemostats on porcine kidney surgical models demonstrated that blood loss decreased similarly after two minutes, however bleeding continued with decreasing rates for the next ten minutes (34). Bang et al. investigated the effects of hemostatic powder on acute gastric bleeding in porcine models and evaluated the lesion sites at 6, 18, 42, 66 hours after the application. When the experimental and control groups were compared, re-bleeding, which did not show a significant difference, was reported. However, significant differences were found in terms of hemostat persistence rates at the sites of injury (35). Tuthill et al. studied on renal excision models of heparinized rats and reported that the liquid fibrin sealant provided more hemostasis ability than the gelatin sponge soaked in thrombin did, and experimental groups provided significant hemostasis compared to the controls (36). Similar to the literature, statistically significant differences were found for the control group when compared to the AHA experimental groups (p=0.001) in this study. The bleeding sites of the rats in the control group were treated with tampon solution, but the bleeding did not stop even after three separate applications every two minutes. Therefore, all rat models in the control group failed hemostasis. Germiyanoglu et al. observed no significant difference between the mean durations of hemorrhage in control and experimental group in their research with a plant-based hemostat applied on rat renal trauma models (37).

This study had some limitations. Firstly, there is no adequate data in the literature on renal venous bleeding models to determine the efficacy and reliability of this model. Secondly, since the rats were used in this study, the hemostatic performance and efficacy of AHA might change when applied to an acute bleeding site in the human body. In addition, the certainty of the statistical results might be affected in this study, considering the small sample size of the investigation. Depending upon factors such as the physical characteristics of the animals, experience of the practitioner, technical differences, variation in vessels or laboratory conditions, the mean duration of bleeding may show alterations, if several other studies are performed on the same model.

Conclusion

The vessel incision model in our study revealed the fast-acting physical hemostatic properties of the liquid and powder formulations of AHA in the renal vein. This natural applicable product could be used to induce hemostasis in rat models of bleeding caused by various renal damages, and it could also prevent local bleeding in humans. More studies are needed to compare the short and long-term efficacy of different formulations of the polysaccharide-based herbal product in various organs and surgical models.

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