Research Article

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Algan hemostatic agent in liver injury

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Histopathological effects of Algan hemostatic agent (AHA) in liver injury model in rats

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Abstract

Background and Aim: In this study, we aimed to assess the hemostatic and histopathological impacts of the Algan hemostatic agent (AHA) with the liver injury model.

Materials and Methods: 24 male rats, 10-12 week old, were randomly divided into three equal groups (n=8) as control (physiological saline solution), AHA liquid and AHA powder. A total of three iatrogenic cut injuries were performed on the anterior surface of the left liver lobe. After bleeding started, sponges soaked with physiological saline, AHA liquid, AHA powder were gently pressed on the injured area for 20 seconds in corresponding groups, respectively. The bleeding time was measured with a timer. Failure to stop bleeding after three consecutive applications was considered as a failure. Animals were euthanized at the tenth minute of the procedure. Left liver lobes were removed for histopathological examination.

Results: Bleeding control success rates of AHA liquid were significantly higher than that of the AHA powder group, and both forms were more effective than physiological saline. A superficial thick granulation tissue with entrapped powder residual materials was detected in the AHA powder group. Liver parenchyma was intact in liquid and powder groups.

Conclusion: AHA is a fast-acting and applicable hemostatic agent in the liver bleeding model. However, further comparative studies in various organs are needed.

Keywords: Algan hemostatic agent; injury; trauma; liver; rat.

Introduction

The liver contains the greatest amount of blood, as its parenchyma consists of a very dense sinusoidal supply. The sinusoidal wall in the liver lacks vasoconstrictor smooth muscle organisation, thus hepatic tissue integrity impairment leads to uncontrolled bleeding. The right lobe of the liver is most affected by trauma, however, the left lobe has more serious clinical consequences and affects adjacent visceral organs. Although the liver trauma-induced mortality rate is 10-15%, the leading mortality factor here is bleeding and its secondary complications.[1] Hepatic bleeding may occur during trauma and surgical procedures including elective primary or metastatic tumor resections, moreover cirrhosis can cause significant blood loss. Reducing blood loss is significant in order not to disrupt the the course of liver surgery or to prevent sudden blood loss in emergencies that cause death. Stitching, which is one of the major methods for bleeding control in the other tissues, is not effective enough in liver tissue, since the tissue has the potential to rupture even when the suture is tied.[2]

Various techniques have been used to perform liver surgeries with less risk, including vascular clamping techniques, the use of various dissection devices, the use of pharmacological agents, the use of topical sealants and hemostatic agents.[3-6] Recently applied alternative therapies include various local hemostatic agents such as collagen, gelatin or cellulose-based products, fibrin sealant, and synthetic glues, which are used in this case as topical operators.[7] Agents such as chitosan, ankaferd, coolclot, fastact, zeolite or algan hemostatic agent (AHA) are among these and are preferred in coagulopathic patients to reduce bleeding and the risk of infection.[8-12] Algan hemostatic agent liquid is a class III hemostatic agent (Certificate number: EC Design-Examination Certificate 1783-MDD-214) derived from a standardized mixture of six different herbs. Each of the plants that make up the AHA has a content that provides hemostasis in combinations. Tested for biocompatibility, this multi-herbal extract has confirmed for its reliability and efficacy, including irritation and hemodynamic testing, thus offering a safe therapeutic alternative.[12]

Moreover, AHA powder is a locally applied, very low-cost, storage-free, herbal-only, class III starch-based absorbable hemostatic agent (Certificate number: EC Design-Examination Certificate 1783-MDD-197). AHA creates thick polymeric networks, a physical barrier in the applied area, and prevents the blood from leaking by trapping blood and its components into these networks, thus ensuring hemostasis.[12] Based on recent studies showing the effects of this new herbal product in various tissues with different surgical models, we aimed to assess its hemostatic impacts and histopathological effects with an experimental liver injury model which causes uncontrolled bleeding in liver tissue.

Materials and Methods

Animals

24 male Wistar Albino rats, 10-12 week old, were used in this research, and animals were obtained from Marmara University Medical School Experimental Animal Breeding and Experimental Research Center, Istanbul, Turkey.. Rats weighing 200–250 g were housed in clean, sterile,

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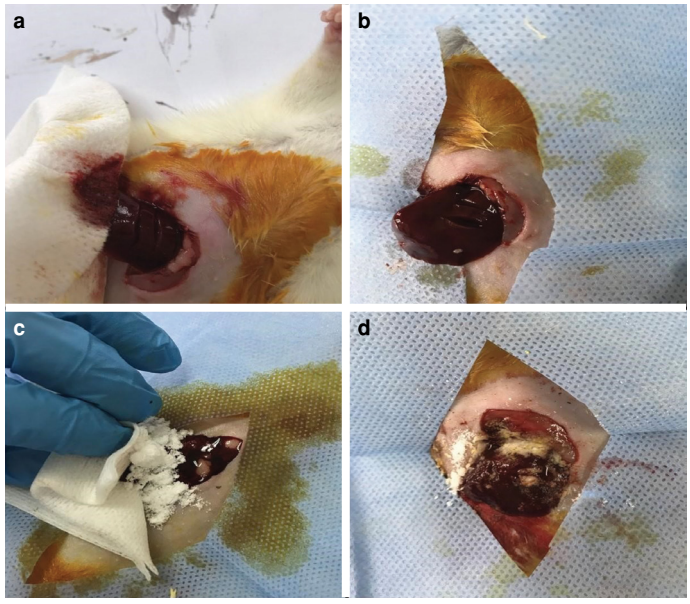

Figure 1. Application of different forms of Algan Hemostatic Agent. Algan Hemostatic Agent (AHA) liquid application after injury created by three cuts on the liver surface **(a)**. Bleeding control after AHA liquid application **(b)**. AHA powder application after injury with three cuts on the liver surface **(c)**. Bleeding control after AHA powder application **(d)**.

polypropylene cages under standard vivarium conditions (12 h light/dark cycles) with free access to water and standard rat chow. The animals were housed in an air-conditioned animal room at 22±3°C and 55±10% humidity. Animal experiments were carried out in accordance with the ethical norms approved by the Local Animal Experiments Ethics Council of Marmara University Istanbul, Turkey (Ethics Committee Approval No:13.2021.mar, Dated:11.01.2021).

Experimental Design, Surgical Procedure and Bleeding Test

Rats were randomly divided into three equal groups with eight animals per group. The groups were randomly designed as the control (treated with physiological saline solution) group, the AHA liquid group, and AHA powder group. Physiological saline (2 ml) and AHA liquid (Algan Group Health Services Import and Export Industry and Trade Limited Company, Istanbul, Turkey) forms (2 ml) were soaked in sponges before the operation. Surgical procedures were carried out under general anesthesia with an intraperitoneal injection of ketamine hydrochloride (Ketalar, Eczacıbaşı, Istanbul, Turkey) of 100 mg/kg and xylazine (Rompun, Bayer, Istanbul, Turkey) of 10 mg/kg. Anesthetic depth was assessed by conventional reflex testing and by monitoring autonomic parameters and movement.[13] Anterior abdominal wall furs were shaved and disinfected with 10% povidone-iodine solution.The abdominal cavity was opened with a 3 cm vertical median incision. A total of three iatrogenic cut incisions, 1 cm in length and 2 mm in depth, were performed on the anterior surface of the left liver lobe. Immediately after the bleeding started, the sponges soaked with physiological saline, AHA liquid were pressed slightly on the injured area for 20 seconds in control and AHA liquid groups, respectively. AHA powder form was applied on the bleeding site for 20 seconds with a mild sponge compress (Fig. 1a). Each application took 20 seconds. The bleeding time was measured with a timer. When the bleeding stopped, it was recorded as the bleeding stopped and in

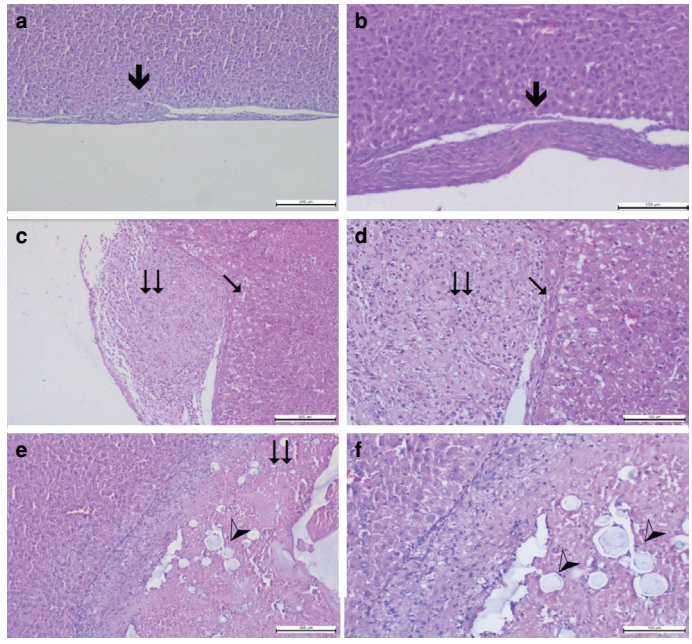

Figure 2. Histopathological evaluation of liver tissue. Photomicrographs showing the thin fibrous band (↑) formation **(a)** and the higher magnification of fibrous band **(b)** in the control group. Superficial granulation tissue (↓↓) overlying the intact liver parenchyma (↘) **(c)** and the higher magnification of granulation tissue **(d)** in the AHA liquid group. Superficial granulation tissue including residual materials (▲) **(e)** and the higher magnification of granulation tissue with residual materials **(f)** in the AHA powder group (Hematoxylin and eosin, Bars: A,C,E: X200 µm and B,D,F: X100 µm).

reverse condition, additional implementation was performed with the same amounts of materials, and the number of the additional applications were recorded with the same durations. Being unable to stop bleeding after three consecutive applications was considered a failure. All animals were euthanized with abdominal bleeding at the tenth minute of the procedure. The left lobes of the liver of the rats in each group were removed for histopathological examination.

Histopathological Analysis

All liver tissue samples were fixed in 10% neutral buffered formalin solution for 72 hours. The samples were dehydrated in elevating ethanol series (70%, 80%, 90% and 100%), then cleared in xylene and embedded in paraffin. The paraffin blocks were cut into 4-5 µm thick sections with a rotary microtome (Thermo Shandon Finesse E). The sections were stained with hematoxylin and eosin (H&E) for histopathological evaluation. The sections were then examined and photographed under a camera-mounted light microscope (Leica DM 2500, Germany; LasV 4.10 program). A semi-quantitative scoring system (1: mild; 2: moderate; 3: severe) was used to assess inflammation status and granulation tissue formation. The residual material was scored from 0 to 3 (0: no damage; 1: mild; 2: moderate; 3: severe). A similar scoring system was used for cell necrosis according to Dorterler et al.[14]

Statistical Analysis

The Pearson Chi-squared test and Fisher exact test (if necessary) were used to analyze categorical variables. Scores were compared among

Table 1. Evaluation of bleeding test results among the groups

	Application result						p
	Positive		Negative		Total		
	n	%	n	%	n	%	
1st application (20 seconds)							<0.001
AHA liquid group	7	87.5	1	12.5	8	100	
AHA powder group	5	62.5	3	37.5	8	100	
Control (serum physiologic) group	0	0	8	100	8	100	
Total	12	50	12	50	24	100	
2st application (20 seconds)							0.003
AHA liquid group	1	100	0	0	1	100	
AHA powder group	3	100	0	0	3	100	
Control (serum physiologic) group	0	0	8	100	8	100	
Total	4	33.3	8	66.7	12	100	
3st application (20 seconds)							nc
AHA liquid group	0	0	0	0	0	0	
AHA powder group	0	0	0	0	0	0	
Control (serum physiologic) group	0	0	8	100	8	100	
Total	0	0	8	100	8	100	
Result							0.001
AHA liquid group	8	100	0	0	8	100	
AHA powder group	8	100	0	0	8	100	
Control (serum physiologic) group	0	0	8	100	8	100	
Total	16	66.7	8	33.3	24	100	

AHA: Algan hemostatic agent.

the three groups using Kruskal Wallis variance analysis. When the differences were found, the difference group was determined by the Mann Whitney test with p values subjected to Finner adjustment. Demographic information was summarized using descriptive statistics (median, [Q1:p25 Q3:p75]) or frequency distribution (n and %), according to the type of data. A two-tailed $p<0.05$ was considered significant for all tests. The Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL) was used to analyze the data of this study.

Results

Bleeding Test Results

The bleeding control success rates of the first 20-second application of the AHA liquid and AHA powder were 87.5% and 62.5%, respectively and the control group's first application success rate was 0%. These results were statistically significantly higher than the physiological saline-administered control group success rate ($p<0.001$). Moreover, comparing the AHA groups, the bleeding control success rates in the first application results of AHA liquid were significantly higher than in the AHA powder group (Table 1). The second 20-second application bleeding control success rates of AHA liquid and AHA powder (100%) were significantly higher than the second application success rate of the control group ($p=0.003$) (Table 1). Consequently, when the success rates were overall examined, the bleeding control success rates in AHA liquid and powder application results (100%) were significantly higher than the control group results (0%) ($p=0.001$) (Fig. 1, Table 1). In the physiological saline solution treated control group, three applications each lasting 20 seconds were failed to stop the bleeding in eight rats.

Table 2. Evaluation of histopathologic scores among the groups

	AHA liquid	AHA powder	Control	p
Necrosis	0 [0 0]	0 [0 0]	0 [0 0]	nc
Inflammation	0 [0 1]	1 [0 1]	0 [0 1]	0.213
Formation of granulation	[a]2 [2 2]	[a]2 [2 3]	[b]1 [1 1]	<0.001
Residual material	[a]0 [0 0]	[b]1 [1 2]	[a]0 [0 0]	<0.001

The values of quantitative variables are given as median and quartiles M[Q1 Q3]. Within each row, the different letters in the superscript indicate significant differences ($p<0.05$) according to the Mann-Whitney test with Finner-adjusted p-values. AHA: Algan hemostatic agent.

Histopathological and Statistical Analysis Results

In the histopathological investigation, thin fibrous band formation was observed on the injured superficial area (Fig. 2a), and the underlying liver tissue parenchyma was intact, necrosis and inflammation were not detected (Fig. 2b, Table 2) in the control group. Superficial granulation tissue was evident in AHA liquid group and was observed

to replenish the injured area (Fig. 2c). At higher magnification, intact liver parenchyma without necrosis and inflammation was seen just beneath the granulation tissue (Fig. 2d, Table 2). Superficial thick granulation tissue was observed in the AHA powder group, and entrapped powder residue materials were also clearly visible within the granulation tissue (Fig. 2e). No foreign body reaction was observed around the residual materials. A thick hystiocytic layer was evident between the granulation tissue and the liver parenchyma, moreover the intact liver parenchyma was clearly separated by granulation tissue at the higher magnification. No necrosis was detected (Fig. 2f, Table 2). The inflammation status of the liver tissue parenchyma of all groups was statistically similar ($p=0.213$) and there was no statistically significant difference between the study groups in terms of necrosis ($p>0.05$). Granulation tissue formation in the AHA liquid and powder groups was significantly higher than in the control group ($p<0.001$). The entrapped powder residual materialsdetected in the AHA powder group were statistically significant ($p<0.001$) than in the other groups (Table 2).

Discussion

Despite the developing technology, the bleeding problem of the liver, which is quite risky, has not been solved yet. AHA, a polysaccharide-based hemostatic agent, creates a highly effective hemostatic barrier in local bleeding by enclosing fibrin, blood and blood components in the environment when poured into the liver injury area in liquid or powder forms. In this study, the hemostatic and histopathological effects of two different formulations of AHA, as powder and liquid, were investigated in post-traumatic rat liver. We compared the bleeding control activities of the powder and liquid forms in our experimental model although, the bleeding control activity of the powder form has been reported faster.[15] In the first and second applications, we obtained high bleeding control efficacy rates in the AHA liquid form.According to previous studies, it is a well-known fact that both AHA forms are effective in reducing blood loss and stopping bleeding in a shorter time compared to control groups.[16] Studies in the literature have shown that bleeding time varies depending on the control group in the study, the experience of the practitioner, technical differences, and laboratory conditions. Akarsu et al. compared the effectiveness of Ankaferd Blood Stopper (ABS) and fibrin adhesive and the results showed that bleeding control was achieved in 18 and 17 seconds, respectively.[17] In our study, bleeding control success rates of the first 20-second application of AHA liquid and AHA powder were 87.5% and 62.5%, respectively. These results suggested that AHA is effective in both forms but AHA liquid form acts faster in the liver trauma model. Another study by Aydin O et al. compared the hemostatic effects of calcium alginate and ABS in hepatic parenchymal hemorrhages and according to the results, although both groups had hemostatic effects, a massive fibrotic area was observed in the fibrotic alginitis group and patchy focal necrosis areas without fibrosis were detected in the ABS group.[18] Distinct superficial granulation tissue in the AHA liquid group and thick superficial granulation tissue with entrapped powder residual materials and underlying thick hystiocytic layer was observed in the AHA powder group in our study. Moreover, liver tissue was intact, necrosis and fibrosis were not observed in either group of this study. In another study to investigate the heparin-influenced hemostatic efficacy of ABS, a group of rats under the influence of the hemostatic agent heparin and another group of rats not under the influence of heparin were compared. In the study groups with the second-degree liver damage, it was reported that heparinization could be useful to ABS in stopping bleeding by a ABS hemostatic effect in the heparinized group as soon as possible.[19] In a study conducted by Adams GL et al. using the pig model, hemostatic effects were compared using Gelfoam plus saline and Gelfoam plus human thrombin in liver laser hemorrhage. Gelfoam plus human thrombin was observed to provide better control of bleeding compared to Gelfoam plus saline.[20] In our study, the groups were designated as physiological saline solution treated non-heparinized control group, AHA liquid, and AHA powder group to compare the efficacy of only AHA product forms without heparinization.

Karakaya et al. showed the beneficial effect of hemostatic agent use with regard to long survival rates after trauma in rats and they determined the experimental duration as 30 minutes or until the death of experimental animals. We euthanized the animals at the tenth minute of the experiment, and according to our observations, the health of the animals was similarly better in the AHA implemented groups than in the control.[21] The results of the drying paper studies in the literature do not provide sufficient benefit and the use of these methods is not recommended. In the results of another study evaluating the new fibrin sealant patch in the control of bleeding after vascular or hepatic injury, it was recorded that vascular damages occurred due to the pressure applied to the area, even though the bleeding was successfully stopped.[22]

Physiological saline and AHA liquid were applied on the injured area with slight press and, AHA powder was applied to the injured area with a mild sponge compress in our study. Besides, the histopathological examination of liver tissues in the control and AHA liquid groups which were exposed to slight press displayed intact liver parenchyma. Segura-Sampedro JJ et al. designed a new vacuum-based device with perihepatic packaging to stop grade IV–V liver hemorrhages without adverse side effects. The device promotes clotting and stopping liver bleeding under pressure by perihepatic packaging. It was also aimed to stop the liver hemorrhage, which was checked about 48-72 hours after the compression placement, otherwise, it has the potential to have quite complex results, but may cause complications again in case of excessive packaging due to surgical experience.[23] In another study comparing surgical hemostatic sponges in liver injuries using the rat model, three different sponge types, namely gelatin, horse collagen and oxidized cellulose, were applied and their hemostatic capacities were compared.[24] Fontes et al. observed that all groups had similar hemostatic effects, however, the gelatin sponge showed more inflammation and adhesion to the structures adjacent to the procedure compared to other groups.[24] We used the solid AHA form as a powder in this study, and according to the histopathological examination, entrapped powder residual materials in the granulation tissue were clearly observed, however, no inflammation was detected in the liver tissues of the AHA powder group. In another study aimed at stopping rat tail bleeding, Saline was compared with the liquid form of AHA, and bleeding that did not stop at 40 seconds was considered as a failure similar to our model. AHA reportedly stopped bleeding in 20 seconds while saline failed.[25] AHA is an exceedingly viable topical hemostatic operator in the liver injury bleeding models and may be a clinically successful choice for the control of bleeding during surgical operations or through other emergencies. Although there are differences in bleeding control times in different ways, the use of AHA as a hemostatic agent would be very beneficial to protect the tissue and control bleeding.

In conclusion, AHA-related surgical injury model and subsequent histopathological investigations revealed the physical hemostasis function of AHA in the liver. With both forms, AHA formed a gel and a barrier in the environment when poured into the liver injury site. It is effective in local bleeding in powder and liquid forms without tissue damage, thus, it is a highly up-and-coming product to control hemostasis of liver injury models in both rats and humans. Additional comparative studies with different products and in various organs are required to prove the beneficial effects of this new polysaccharide-based herbal hemostatic agent.

Ethics Committee Approval: The Marmara University Local Animal Experiments Ethics Committee granted approval for this study (date: 11.01.2021, number: 13.2021.mar).

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Conflict of Interest: The authors have no conflict of interest to declare.

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