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Comparison of hemostatic and acute histopathological effects of Algan Hemostatic Agent in experimental liver lobectomy model in rats

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Abstract

Aim: Algan Hemostatic Agent (AHA) is a plant-based material effective in hemostasis. The purpose of this study was to compare the hemostatic efficacy and acute histopathological effects of liquid and powder forms of AHA in rat model of experimental liver lobectomy.

Methods: Twenty-four male Wistar albino rats, 10-12 weeks old, were randomly divided into three groups (n=8): control (physiologic saline), AHA-liquid, and AHA-powder. Following the resection of the outer one-third of the left hepatic lobe, physiological saline, liquid and powder, was administered to the injured area for twenty seconds. At the tenth minute, all animals were sacrificed through intra-abdominal bleeding. Liver tissues from all groups were excised for histopathological analysis.

Results: Bleeding control success rates of the first application results of AHA-liquid were higher than those of AHA-powder. Success rates of the second application of AHA liquid (66.6%) and AHA powder (50%) were substantially higher than those of the control group. The liver parenchyma was intact, and a dense fibrous tissue capsule was noted at the wound site of the liquid group. In powder group, late granulation tissue was observed along with moderate lymphocyte infiltration and some powder remnants.

Conclusion: The present study showed that herb-based AHA is an effective material for controlling blood loss in liver lobectomy model. It formed a stable clot without causing damage to liver tissue, especially when administered in liquid form. AHA could be a preferred and promising option for managing hemorrhage during crucial operations due to its biocompatibility and rapid efficacy.

Keywords: Algan Hemostatic Agent, liver lobectomy, histopathology, bleeding, rat

Introduction

Hepatic lobectomy, a surgical procedure involving the removal of a portion of the liver, is a critical intervention employed in the treatment of various hepatic pathologies, including primary and metastatic liver tumors, traumatic injuries, and complex congenital anomalies (1, 2). The success of hepatic lobectomy depends not only on the surgeon's skill but also on the effective management of intraoperative and postoperative bleeding, which can be a challenging and potentially life-threatening aspect of the procedure (3). Due to the absence of vasoconstricting smooth muscle fibers in the sinusoidal structure of the liver parenchyma, it is difficult to control hemorrhage when hepatic tissue integrity is impaired (4, 5). Pressure, clamping, the use of dissection devices, and topical hemostatics are leading methods for achieving a hemostatic state (2). Hemostatic agents play a pivotal role in achieving optimal outcomes by controlling hemorrhage, reducing the risk of postoperative bleeding, and reducing the associated morbidity and mortality (6). These agents are widely utilized in medical practice with many alternatives. In recent years, there has been a growing interest in the development and utilization of hemostatic agents in the field of hepatic surgery. The selection and application of the most appropriate hemostatic agent are influenced by various factors such as the extent of liver resection, underlying liver disease, patient comorbidities, and the surgeon's preference (7). Several types of topical hemostatic agents commonly used in liver lobectomy are absorbable and flowable agents, fibrin sealants, fibrin glues, and hemostatic sponges (4, 8).

The Algan Hemostatic Agent (AHA) is a standardized herbal extract consisting of six separate plants: blackberry leaf (8%), walnut leaf (10%), mistletoe plant (35%), yarrow (25%), wolf claw (7%), and grape leaf (15%). Each of the plants constituting the AHA is efficacious on endothelial cells, blood cells, vascular formation (angiogenesis), vascular dynamics, and mediators, and has hemostatic and wound-healing properties (9-11). Algan has been evaluated for biocompatibility and proven reliable and effective in irritant and hemodynamic tests, providing a safe treatment option (12). AHA powder is a class III starch-based absorbable local hemostatic agent with no storage requirements, and AHA liquid is a flowable hemostatic agent; both are certified for quality assurance. AHA was tested on numerous organs, including the liver, kidney, and spleen (5, 13, 14), using various surgical models, but there was no study in the literature that evaluated the acute efficacy of AHA in the liver lobectomy model. The purpose of this study was to investigate the hemostatic efficacy and acute histopathological effects of liquid and powder forms of AHA in rat model of experimental liver lobectomy.

Materials and Methods

Animals and study design

Twenty-four male 10- to 12-week-old Wistar albino rats weighing between 250-280 g were used in this study, and the animals were obtained from the Marmara University Medical School Experimental Animal Breeding and Experimental Research Centre, Istanbul, Turkey. Animal experiments in this study were performed with the ethical norms approved by the Local Animal Experiments Ethics Council of Marmara University (2021/05). The rats were kept in clean polypropylene cages with free access to water and standard rat chow under standard vivarium conditions (12 h light/dark cycles) in a temperature-controlled and humidified animal room. Rats were then randomly divided into three groups of eight animals each according to a previous study (5). Groups were designed as control (physiological saline solution), AHA-liquid, and AHA-powder. Physiological saline (2 ml) was immersed in gauze patches, AHA liquid (Algan Group Health Services Import and Export Industry and Trade Limited Company, Istanbul, Türkiye) (2 ml) was prepared in an injector prior to surgery, and AHA powder (2 g) was available for use. A graphical illustration of the study design is shown in Figure 1.

Surgical procedure and Bleeding test

All groups underwent surgical procedures under general anesthesia with intraperitoneal injections of 100 mg/kg ketamine hydrochloride (Ketalar, Eczacıbaşı, Istanbul, Turkey) and 10 mg/kg xylazine (Rompun, Bayer, Istanbul, Turkey). Anesthetic depth was determined by monitoring skin/finger pressure responses, palpebra and corneal reflexes, heart rate, respiratory rate, and other physiologic activities. The anterior abdominal wall furs of all rats were shaved and disinfected with a 10% solution of povidone-iodine. The abdomen was opened 3 cm with a midline incision, and following the opening of the peritoneal cavity, the outer one-third of the left lobe of the liver was removed (Fig. 2a). Physiologic saline-immersed gauze (Fig. 2b), AHA liquid (Fig. 2c), and AHA powder (Figs 2d, e) were rapidly applied to the wounded site of the respective groups for a duration of twenty seconds, following the onset of bleeding. At the 20-second mark of the chronometer, the hemorrhaging site was examined. If bleeding did not stop after 20 seconds, the procedure was repeated with the same amount of material, and the number and outcomes of the subsequent applications were recorded. Hemostasis not achieved after the third application in each group was recorded as “failed." At the tenth minute, all animals were sacrificed by intra-abdominal bleeding. Liver tissues from all groups were removed for histopathological analysis.

Histopathological analysis

All liver tissues were preserved in 10% neutral buffered formalin solution for 72 hours and washed with tap water. Standard tissue processing was performed as described in the literature (15). The samples were dehydrated in a gradually ascending ethanol series, then cleared with xylene and embedded in paraffin. Using a rotary microtome (Thermo Shandon Finesse E), the paraffin blocks were cut into 4-5 µm thick sections. Then, they were stained with hematoxylin and eosin (H&E) for histopathological evaluation. Preparations were examined and photographed using camera-equipped light microscope (Leica DM 2000, Germany; LasV 4.10 program). A semi-quantitative scoring system (0: no damage, 1: mild, 2: moderate, 3: severe) was utilized to evaluate cell necrosis, inflammation status, granulation tissue formation, and residue reaction (5).

Statistical analysis

Analyses were performed by using IBM SPSS 25.0 software (IBM Inc., Armonk, New York, USA).

The Pearson Chi-squared test and Fisher exact test were used to evaluate categorical variables in the bleeding test results. Histologically scored data were subjected to a non-parametric Kruskal-Wallis analysis of variance, while multiple comparisons between groups were analyzed using Tamhane's T2 post-hoc test. The scoring results were presented as quartiles (M: p50[Q1: p25 Q2: p75]), and the bleeding evaluations were presented as a frequency distribution (n and %). $p<0.05$ was considered statistically significant.

Results

Bleeding test results

The results of the first 20-second AHA liquid (Fig. 2c) and AHA powder (Figs. 2d, e) (62.5% and 50%, respectively) applications were statistically significantly higher than the control application (0%) (Fig. 2b) ($p<0.05$). Moreover, when the AHA groups were compared, bleeding control success rates of the first application results of AHA-liquid were higher than those of AHA-powder (Table 1). Similar to the initial application, the success rates of the second application of AHA liquid (66.6%) and AHA powder (50%) were higher than those of the control group. However, the difference in percentages is not statistically significant ($p=0.233$) (Table 1). In the third application, all remaining animals in the AHA groups were successfully controlled for hemorrhage (Table 1). The liquid form affected more animals in less time, and the AHA groups successfully halted the bleeding after three consecutive 20-second applications ($p<0.001$). Nevertheless, three applications in the control group failed to stop the bleeding (Table 1).

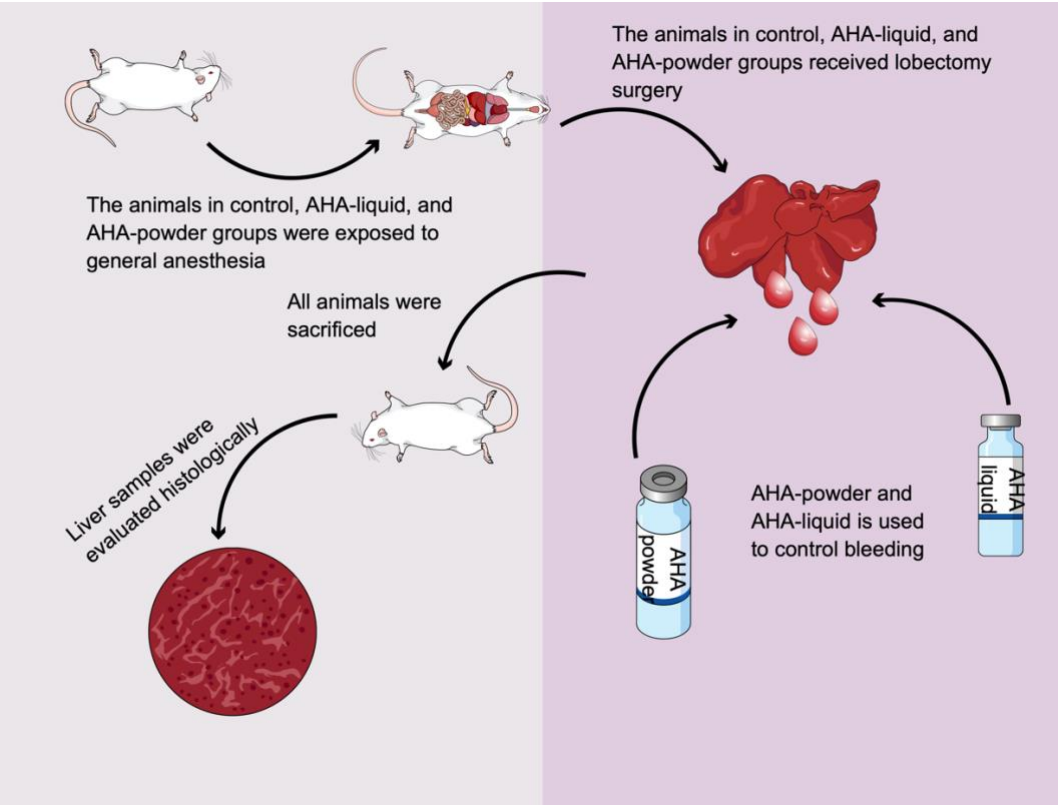

Figure 1. Graphical illustration of the study.

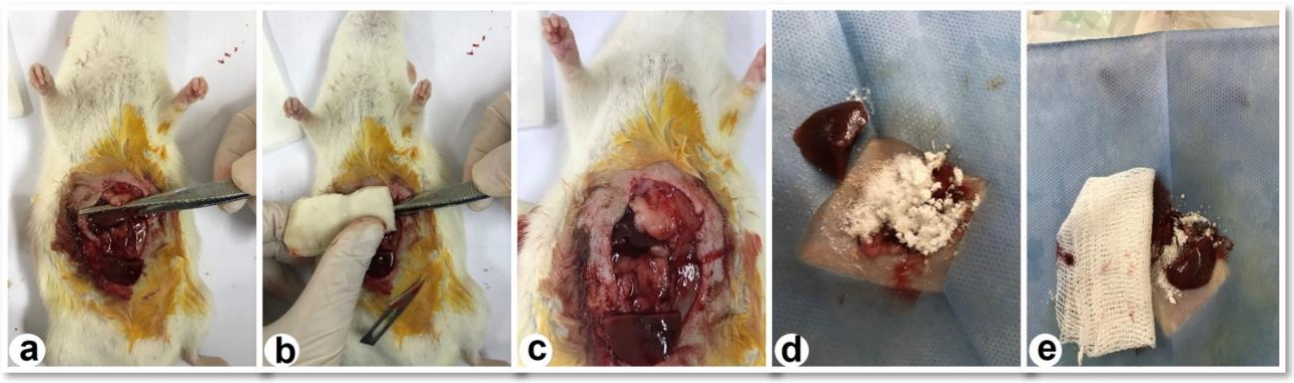

Figure 2. The image shows liver lobectomy procedure in the control group (a). Application of Algan Hemostatic Agent (AHA) in liquid form (b) and subsequent control of bleeding (c) in lobectomized rats in the AHA liquid group. AHA powder form application (d) and subsequent bleeding control (e) in lobectomized rats in the AHA powder group.

Histopathological Examination Results

Histopathologic examination of the control group revealed a thin layer of fibrous tissue over the injury site along with minimal inflammation and underlying intact liver parenchyma (Figs. 3a, d). Dense fibrous tissue and intact liver parenchyma were observed on the surface of the AHA liquid group, inflammation was minimal and comparable to the control group (Figs. 3b, e). The AHA powder group showed dense fibroblastic proliferation, resulting in the formation of a fibrous band or late granulation tissue. Locally, powder residues were observed within the granulation tissue (p<0.01). In addition, granulation tissue was adequately separated from liver parenchyma. Hepatocytes beneath the granulation tissue (Figs. 3f) showed vacuolation, and the parenchyma and granulation tissue displayed moderate inflammation (Figs. 3c, f). There was no evidence of necrosis in any of the groups. There was a minimal difference between the groups in terms of inflammation. Mild to moderate inflammation was observed in all study groups (p<0.001) (Table 2).

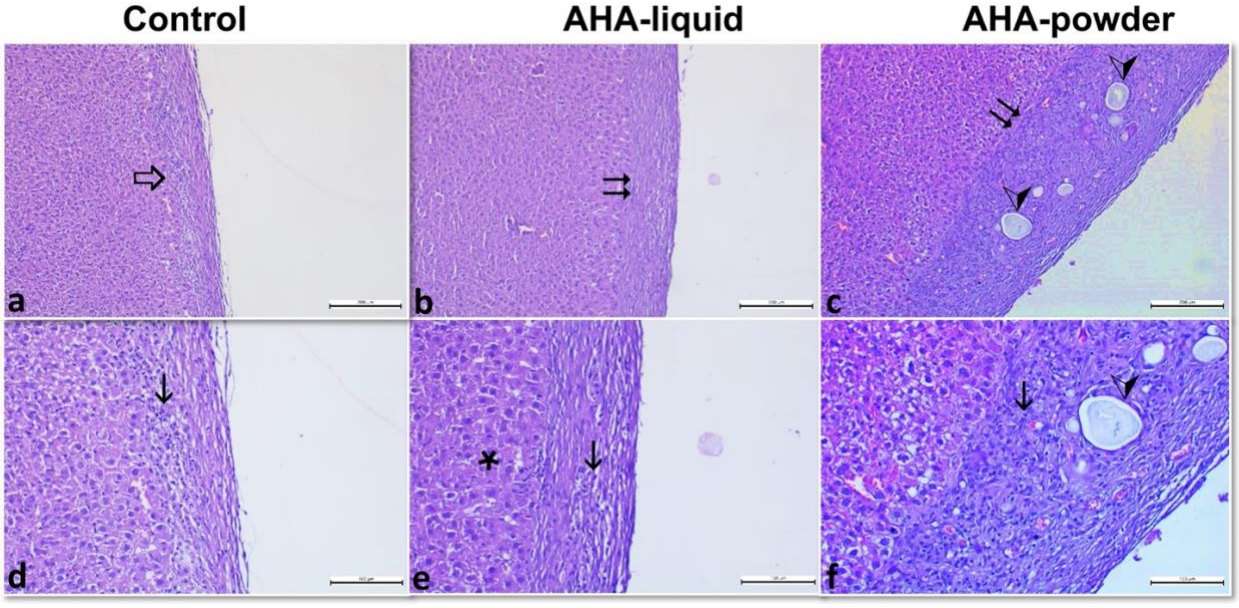

Figure 3. Photomicrographs of control (SF) group showing the thin fibrous tissue (⇨) organisation on the liver surface (a) and lymphocyte cell infiltration (↓) inside the fibrous tissue (d). Superficial late stage granulation tissue (⇉) (b) overlying the intact liver parenchyme (★) and lymphocyte cell infiltration (↓) inside the late stage granulation tissue (e) in the AHA-liquid group. Powder residues inside (⩛) the organised superficial granulation tissue (c) and lymphocyte infiltration (↓) (f) in the AHA-powder group (Hematoxylin and eosin, Bars: a, b, c: X200 µm and d, e, f: X100 µm).

Table 1. Bleeding test results of control, AHA liquid and AHA powder groups

	Application result						*p*
	Positive		Negative		Total		
	n	%	n	%	n	%	
1st application							
AHA liquid group	5	62.50	3	37.50	8	100	*<0.05*
AHA powder group	4	50.00	4	50.00	8	100	
Control group	0	0.00	8	100.00	8	100	
Total	9	37.50	15	62.50	24	100	
2nd application							
AHA liquid group	2	66.66	1	33.33	3	100	*0.233*
AHA powder group	2	50.00	2	50.00	4	100	
Control group	0	0.00	8	100.00	8	100	
Total	4	38.89	11	61.11	15	100	
3rd application							
AHA liquid group	1	100.00	0	0.00	1	100	*nc*
AHA powder group	2	100.00	0	0.00	2	100	
Control group	0	0.00	8	100.00	8	100	
Total	3	66.67	8	33.33	11	100	
Result							
AHA liquid group	8	100.00	0	0.00	8	100	*<0.001*
AHA powder group	8	100.00	0	0.00	8	100	
Control group	0	0.00	8	100.00	8	100	
Total	16	66.67	8	33.33	24	100	

$p<0.05$ was considered as statistically significant according to Pearson Chi-squared test and Fisher exact results of bleeding tests. AHA: Algan Hemostatic Agent, nc: No statistics are computed.

Table 2. Evaluation of necrosis, inflammation, granulation and residual material scores in control, AHA liquid and AHA powder groups.

	Control	AHA liquid	AHA powder	*p*
Necrosis	0 [0 0]	0 [0 0]	0 [0 0]	*nc*
Inflammation	1 [1 1]^a	0 [1 1]^a	1 [2 3]^b	*<0.001*
Formation of granulation	2 [1 2]^a	2 [2 3]^a	1 [1 1]^b	*<0.05*
Residual material	0 [0 0]^a	0 [0 0]^a	2 [1 2]^b	*<0.01*

Scoring results are shown as Q2[Q1 Q3]. Different symbols above the results in each row indicate $p<0.05$ and significance between groups according to Kruskal Wallis variance analysis and post-hoc Tamhane's T2 test. AHA: Algan Hemostatic Agent, nc: No statistics are computed.

Discussion

Liver lobectomy is the commonly preferred surgical technique when particular conditions, including primary and metastatic liver malignancies, traumatic injuries, and congenital anomalies, must be addressed (16). One of the primary determinants that affects the success of a lobectomy is to control intraoperative and postoperative hemorrhage, which is a serious risk for survival (4, 16). In this study, we compared the hemostatic effectiveness and histological consequences of liquid and powder forms of AHA using a hepatic lobectomy model in rats.

In a liver resection model, Roozen et al. investigated the hemostatic effects of Tachosil, Veriset, and NHS-functionalized polyoxazoline (POx). Their results showed that NHS-POx exhibited a substantially shorter hemostasis time (20.4 s) than Tachosil (95.4 s). Additionally, results indicated that Veriset (17.0 s) demonstrated substantially faster hemostasis than Tachosil (17). We determined that the liquid form of Algan achieved 62.5% hemostasis in five animals, and the powder was 50% effective in four subjects within the first 20 seconds of application. Our results were statistically significant, and they were consistent with those of other agents. Another study on the hemostatic properties of microporous polysaccharide hemispheres (MPH), n-butyl-2-cyanoacrylate, and fibrin adhesives in a rat hepatic injury model revealed that hemostasis was achieved within six minutes, twenty seconds, and one minute, respectively (18). Similar to the fibrin adhesive, we detected that all Algan groups ceased bleeding within a minute. According to a study that examines the hemostatic efficiency of modern topical sealants on liver resection model in swine, the avarage time to reach hemostasis of Tachosil, Tissucol Duo, Coseal, and Floseal was 30 seconds, 166 seconds, 95 seconds, and 163 seconds, respectively (19). Our study used a rat model, and AHA exhibited a longer hemostasis duration than Tachosil and a shorter duration than Coseal. According to a previous study on AHA, the liquid form was more effective in halting bleeding than the powder form within the first two minutes of application in a severe rat renal vein hemorrhage model (20). In our initial application results, Algan exhibited similar and expedited outcomes to other agents in the literature. These results demonstrated that both forms of Algan were efficacious, and the liquid form was more rapid in the liver lobectomy model.

There is a limited number of studies that histologically investigate the hemostatic effects of agents on liver lobectomy, according to the literature. Additionally, the experimental models, postoperative periods, and hemostatic agents varied among studies. The efficacy of calcium alginate was studied on hepatic parenchymal bleeding, and histological examinations showed that intense fibrosis was present between the liver, the surrounding tissues, and the calcium alginate fibers, and inflammatory cells encircled the material. Nevertheless, fibrosis was restricted to the liver surface, while deep parenchyma showed no signs of fibrosis (21). Similar to this study, we observed mild inflammation and a thick fibrous tissue organization on the surface of the liver in the AHA liquid group. The tissues examined in the AHA powder group exhibited moderate inflammation and a septal reaction. The liver parenchyma remained intact in both groups. Another hepatic parenchymal study on Ankaferd blood stopper and calcium alginate has revealed that calcium alginate fibers remained on the incision line and caused massive fibrosis, while Ankaferd causes patchy focal necrosis areas but no fibrosis (22). In our study, we detected powder residues in the superficial granulation tissue, which may related to elevated inflammation scores. In another study examining the effects of AHA on liver injury, inflammation beneath the granulation tissue was detected in the AHA liquid group, and superficial thick granulation tissue was detected in the AHA powder group (5). Midi et al. reported mild portal inflammation in all forms of AHA groups in the hepatectomy model in rats (23). Ozemir et al. administered solid carbon dioxide as a hemostatic agent in the hepatoctemy model. Slight to moderate portal inflammation, necrosis, and sporadic fibrosis were reported in contact liver surface (24). Similar to other studies, we observed fibrosis in both groups and mild to moderate inflammation; however, necrosis was not observed.

Conclusion

In conclusion, the use of Algan Hemostatic Agent in lobectomy bleeding has demonstrated its potential as an effective solution for controlling blood loss. Our research has shown that it is capable of promptly terminating hemorrhage and establishing a stable clot without causing any damage to liver tissue, particularly when administered in liquid form. AHA is a promising option for the management of hemorrhage during critical operations, such as lobectomy, due to its biocompatibility and rapid action. Further studies are required to verify its efficacy in a variety of surgical settings, tissues, and bleeding intensities, as well as to investigate its long-term outcomes in order to ensure its broad availability in clinical practice.

Disclosures

Ethical Approval: Ethics committee approval was received for this study from the Marmara University, Local Animal Experiments Ethics Council, in accordance the World Medical Association Declaration of Helsinki, with the approval number: 2021-05.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.Ş.A.; Design – D.Ş.A., D.M.; Supervision – D.M., M.M.; Materials – D.Ş.A., M.M.; Data collection &/or processing – M.M., K.G.; Analysis and/or interpretation – D.Ş.A., K.G.; Literature search – D.Ş.A.; Writing – D.Ş.A.; Critical review – D.M, K.G.

Conflict of Interest: There is no any conflict of interest.

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