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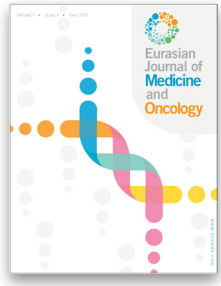


Research Article

# Investigation of the Efficacy of Algan Hemostatic Agent in Liver Laceration Model in Rats

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## Abstract

**Objectives:** Bleeding control is crucial in preventing negative consequences by reducing blood loss in surgical operations. The aim of this study is to evaluate the hemostatic effect of a new herbal hemostatic agent called Algan Hemostatic Agent (AHA) in an uncontrolled bleeding model made by liver laceration.

**Methods:** In these study 5–7 weeks-old 64 rats were used. Rats were randomly divided into 8 groups each consisting of eight rats (4 groups heparinize and 4 groups non-heparinize). The experimental liver laceration was performed, and physiological serum impregnated gauze was applied to the control group for hemorrhage control, AHA liquid form impregnated gauze, AHA gel, and AHA powder form were applied to experimental groups, respectively.

**Results:** The shortest bleeding time was found in the AHA powder group. The AHA powder form stopped the bleeding in the heparinize group for a mean of 4 s, the non-heparinized group for 2 s. This was followed by the gel group and the liquid group. The bleeding time was significantly shorter in the all AHA group compared to the control group.

**Conclusion:** This study showed that AHA is a highly effective hemostatic agent in controlling bleeding compared to the control group.

**Keywords:** Algan hemostatic agent, laceration, liver, rat

Stopping bleeding is crucial in preventing negative consequences by reducing blood loss in surgical operations, especially in the military field or other emergencies. Therefore, in general, extracorporeal injuries, traumatic incisions, breaks and fractures, dental operations, minor and major injuries that occur after spontaneous or surgical interventions, are needed to be stopped by external agents.

When hepatic tissue integrity is impaired, hemorrhage control is difficult because the sinusoidal structure is absent from smooth muscle fibers being in normal vessels.[1, 2] The mortality due to liver trauma is 10–15% and bleeding is the most important factor.[3] Likewise, bleeding and secondary complications are the most important problems in elective surgical resection for primary or metastatic liver tumors.[4]

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**Table 1.** Algan Hemostatic Agent product composition

| The name of the plant | English name | Used part |
|---|---|---|
| Achillea millefolium | Yarrow | Flower |
| Juglans regia | Walnut | Leaf |
| Lycopodium clavatum | Club moss | Whole plant |
| Rubus caesius, R. fruticosus | Blackberry | Leaf |
| Viscum album | European mistletoe | Whole plant |
| Vitis vinifera | Vine | Leaf |

To make liver surgery more safely and shorten the duration of the bleeding time, bipolar and monopolar electrocautery, ultrasonic analyzers, radio frequency equipment, cryotherapy, and various hemostatic agents are used.[5–19] Alternative therapies include local hemostatic agents that reduce bleeding and reduce post-injury complications such as infection.[20] These agents are different products such as collagen, gelatin or cellulose-based products, fibrin sealant, and synthetic glues, which are used as topical agents, especially in coagulopathic patients, in addition to traditional surgical techniques.[13, 20]

The Algan Hemostatic Agent (AHA) is the herbal extract derived from the standardized blend of six different plants (Table 1). As we know, it is the first and only patented product made solely of herbs, with no additives in the world (Patent Application No.: A2015/00018, date of application: 2015/01/05, application publication date: 2016/07/21, application publication no. TR2015 0018 A2, date of issue of patent document: 2017/11/21).

Each of the plants that form AHA has a content which is effective in hemostasis by alone or in combination. All biocompatibility tests such as sensitization, cytotoxicity, and irritation, and hemodynamic tests of the AHA were performed, and the results supported its safety and efficacy as a hemostatic agent. It is easily applied locally. Further, it has low cost and does not require special storage. Apparently, AHA shows its hemostatic effect by forming thick polymeric webs where applied. AHA creates a physical barrier in the bleeding zone, trapping blood, and blood components passively into these nets.

The aim of this study is to evaluate hemostatic efficacy and histopathological effects of AHA in a liver laceration bleeding model.

## Methods

For this study, approval was obtained from Kırıkkale University Animal Experiments Local Ethics Committee (Decision no. 2018/05). The experiment was carried out as described in the literature.[13] In the study, 5–7 weeks old, 180–210 g weighted 64 rats were used. Rats were fed ad libitum and examined under standard laboratory conditions for 12 h dark-light period. At first, the rats were randomly divided into heparinized and non-heparinized groups, each containing 32 rats. Subsequently, the subjects were randomly selected and divided into eight groups each containing eight rats. Heparinized group was administered heparin at a dose of 640 IU/kg intraperitoneally for 3 days, 3 times a day. The same amount of saline was given to the other group.

The groups were formed as follows: Group 1 (Heparinized control group), Group 2 (Heparinized AHA powder group), Group 3 (Heparinized AHA gel group), Group 4 (Heparinized AHA liquid impregnated sponge group), Group 5 (Non-heparinized control group), Group 6 (Non-heparinized AHA powder group), Group 7 (Non-heparinized AHA gel group), and Group 8 (Non-heparinized AHA liquid impregnated sponge group).

Procedures were performed under general anesthesia with ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (10 mg/kg). To perform the experiment, the abdomen was opened 3 cm with the midline intersection. Following the opening of the animal's peritoneal cavity, a total of three iatrogenic lacerations, 1 cm in length and 2 mm in depth, were implanted in the left lobe of the liver anteriorly (Fig. 1). After bleeding start in 2 cc volume of AHA fluid (sponge), AHA powder, AHA gel, and Serum Fizyolojik (SF) impregnated sponge were applied to the liver surface. AHA powder was applied directly to the bleeding surface by hand and not pressed on. The gel form is in liquid form in the injector and sprayed directly into the bleeding area, rapidly gelled after spraying and not pressed on. The liquid form is applied directly to the bleeding surface in the form of a liquid-impregnated sponge and pressed on lightly. In

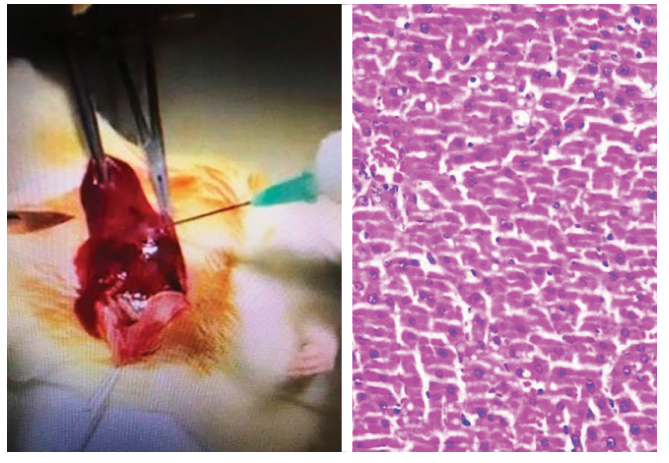

**Figure 1.** (a) Algan Hemostatic Agent (AHA) gel application after three incisions made in liver, (b) parenchymal view (hematoxylin and eosin stain ×400) showing no negative effect of AHA forms applied to the liver on liver healing.

the situation of the continuance of the bleeding, the procedure was repeated with the same amount of product. The first application lasts 15 s, the second application takes 30 s, and the third and subsequent applications take 1 min because it is known that AHA can control the bleeding in about 10 s. The application is measured by chronometry. After the procedure, hemostasis was observed in each group for 10 min. At the end of the procedure, the heparinized 32 rats were aborted with intraabdominal high bleeding. Remnant liver tissue was resected for histopathological research of the acute effects of AHA on liver and placed in 10% formaldehyde solution for fixation.

Non-heparinized 32 rats were kept alive for another week and then their liver was removed for histopathologic examination.

### Histopathologic Investigation

Tissue specimens were routinely processed in the pathology laboratory and examined under a light microscope. These procedures were briefly carried out as follows: The tissue was followed by routine tissue fixation in neutral buffered formalin for a period of time, dehydrated in graded alcohols and embedded in paraffin. 5 mm thick tissue sections were cut and stained with hematoxylin and eosin. Under the light microscope, liver necrosis and inflammatory changes and the presence of AHA residues were assessed.[21]

Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL) was used to analyze the data of this study. Weight and bleeding time were calculated and mean values were compared among the four groups using variance analysis (ANOVA). When differences were found, the difference group was determined by Duncan's multiple range test. The results were assessed at a 95% confidence interval and a significance level of $p<0.05$.

## Results

There was no difference in body weight between the groups ($p>0.05$). The shortest bleeding time was measured in the AHA powder group. The AHA powder form was able to control the bleeding in heparinized and non-heparinized groups in 4 and 2 s, respectively. The AHA gel form was able to control the bleeding in heparinized and non-heparinized groups in 5 and 3 s, respectively. In the AHA non-heparinized liquid group, bleeding control was achieved at 4 rats and 4 rats in the first (15 s) and second (45 s) applications, respectively.

AHA heparinized liquid group, bleeding control was provided at 1, 4, and 3 rats in the first, second, and third application, respectively (Table 2). The bleeding time in the control group was significantly longer than in the experimental groups ($p<0.01$) (Table 2).

AHA powder, AHA gel, and liquid form stopped the bleeding with only one application in all rats. The SF impregnated sponge was applied to the lacerated liver surface at least 4 times for maximum 9 times.

Average bleeding time, body weight of the groups was summarized in Table 2. Hemostasis duration of the control and the AHA liquid groups was reported in Table 3.

In the histological examination of the first application, the hemostatic barrier was observed on the cutted surface of the liver that consists of gel and clot mixture (Fig. 2). 1 week later, the gel form was nearly absorbed, and the macrophage layer was observed between the liver parenchyma and the hemostatic barrier. No necrosis was observed in the liver parenchyma under the macrophage barrier. The hemostatic barrier was seen to be started organizing (Figs. 3 and 4). When hematoxylin and eosin-stained tissue specimens assessed under light microscopy, mild inflammation was observed in AHA liquid, AHA-powder, AHA-gel, and control Group 2 (12.5%), 3 (18.75%), 3 (18.75%), and 2 (12.5%), respectively. Serious inflammation was not noted in any of the control and AHA rats. Light necrosis was observed in AHA liquid, AHA-powder, AHA-gel, and control Group 2 (12.5%), 2 (12.5%), 3 (18.75%), and 2 (12.5%), respectively. Serious and mild necrosis was not noted in any of the control and AHA rats (Figs. 3, 4 and Table 4). There was no statistically significant differences between AHA

**Table 2.** Weight distribution of mean bleeding time, body weight, and resected liver segments for the groups

| Parameters | Group 1 (HC) | Group 2 (HP) | Group 3 (HG) | Group 4 (HL) | Group 5 (NHC) | Group 6 (NHP) | Group 7 (NHG) | Group 8 (NHL) | p |
|---|---|---|---|---|---|---|---|---|---|
| AW (g) | 178.4 | 183.5 | 179.2 | 184.9 | 175.6 | 183.4 | 178.9 | 185.3 | p>0.05 |
| ARLS (mg) | 0.42 | 0.44 | 0.43 | 0.40 | 0.41 | 0.42 | 0.40 | 0.39 | p>0.05 |
| BT (s) (min-max) | 370 (250–535) | 4 (1–7) | 5 (6–9) | <75 (45–105) | 180 (135–320) | 2 (1–4) | 3 (4–7) | <45 (15–45) | p<0.001 |
| ARP (min-max) | 9 (6–12) | 1 | 1 | 2.5 (2–3) | 6 (4–8) | 1 | 1 | 1.5 (1–2) | |

HC: Heparinize control group; HP: Heparinize AHA powder group; HG: Heparinize AHA gel group; HL: Heparinize AHA liquid impregnated sponge group; NHC: Non heparinize control group; NHP: Non heparinize AHA powder group; NHG: Non heparinize AHA gel group; NHL: Non heparinize AHA group of liquid impregnated sponge; AHA: Algan Hemostatic Agent; ARP: Average repetition of process ARLS: Average resected liver segment; AW: Average weight; BT: Bleeding time.

**Table 3.** Control and AHA liquid groups homeostase time

| Groups | 1. Application (15 s) bleeding that stop | 2. Application (30 s) bleeding that stop | 3. Application (60 s) bleeding that stop | 4. and fail | Average repetition of process (min-max) | Average bleeding time (s) (min-max) |
|---|---|---|---|---|---|---|
| NHC | 0 (0%) | 0 (0%) | 0 (0%) | 8 (100%) | 6 (3–8) | 180 (135–320) |
| NHL | 4 (50%) | 4 (50%) | 0 (0%) | 0 (0%) | 1.5 (1–2) | <45 |
| HC | 0 (0%) | 0 (0%) | 0 (0%) | 8 (100%) | 9 (5–12) | 370 (250–535) |
| HL | 1 (12.5%) | 4 (50%) | 3 (37.5%) | 0 (0%) | 2.2 (1–3) | <75 |

Formulation recurrence number formula=(1×1 application number)+(2×2 application number)+(3×1 application number): Total application number, Formula=(15×1 application number)+(30×2 application number)+(60×3 application number): Total number of applications; NHC: Non heparinize control group; NHC: Non heparinize control group; HC: Heparinize control group; HL: Heparinize AHA liquid impregnated sponge group; AHA: Algan Hemostatic Agent.

**Table 4.** Histopathologic evaluation and AHA residues result at the 7th day

| Necrosis | Histopathologic evaluation grading (%) | AHA liquid (%) | AHA powder (%) | AHA gel (%) | Control (%) | p |
|---|---|---|---|---|---|---|
| | No necrosis | 10 (62.5) | 9 (56.25) | 8 (50) | 10 (62.5) | >0.05 |
| | Focal, minimal (1) | 4 (25) | 5 (31.25) | 5 (31.25) | 4 (25) | |
| | Light (<25) | 2 (12.5) | 2 (12.5) | 3 (18.75) | 2 (12.5) | |
| | Mild (25–50) | 0 | 0 | 0 | 0 | |
| | Serious (>50) | 0 | 0 | 0 | 0 | |
| Inflammation | No inflammation | 1 (6.25) | 0 | 0 | 1 (6.25) | >0.05 |
| | Focal, minimal (1) | 5 (31.25) | 3 (18/75) | 4 (25) | 5 (31.25) | |
| | Light (<25) | 8 (50) | 10 (62.5) | 9 (56.25) | 8 (50) | |
| | Mild (25–50) | 2 (12.5) | 3 (18.75) | 3 (18.75) | 2 (12.5) | |
| | Serious (>50) | 0 | 0 | 0 | 0 | |
| AHA residues | | 0 | 80 | 100 | | |

AHA: Algan Hemostatic Agent.

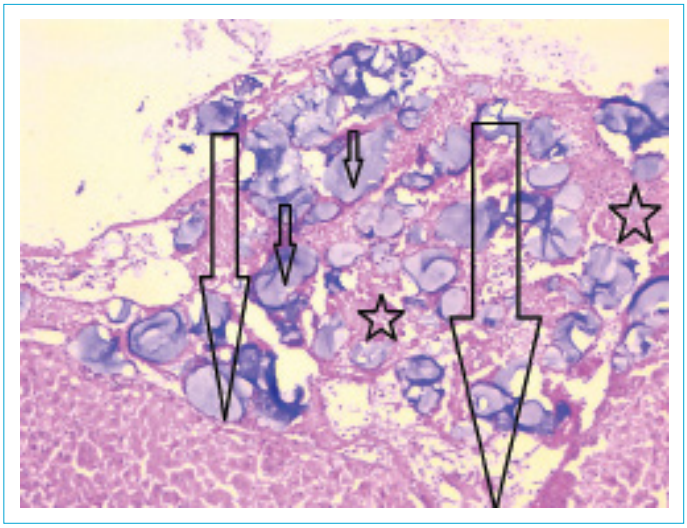

**Figure 2.** The barrier formed on the surface of the liver incision line immediately after application of the Algan Hemostatic Agent (AHA) gel form. It is seen that the gel particles trap the blood between them and form a barrier, Arrow: AHA gel material, Star: Fibrin, blood, and blood elements trapped in the gel material are visible, Long arrow: Normal liver image without necrosis and inflammation (hematoxylin and eosin stain ×100).

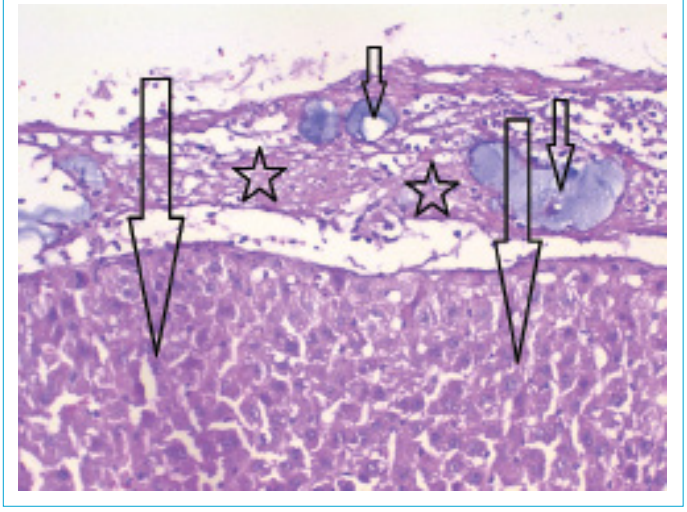

**Figure 3.** Histopathological appearance of Algan Hemostatic Agent (AHA) gel treated liver a week after the procedure, Star: Early organized image forming barrier of AHA gel form on the surface of the liver incision line, Short arrow: AHA gel residue in the mucoid appearance at the site of application, Long arrow: Normal liver image without necrosis and inflammation (Hematoxylin and Eosin stain ×40).

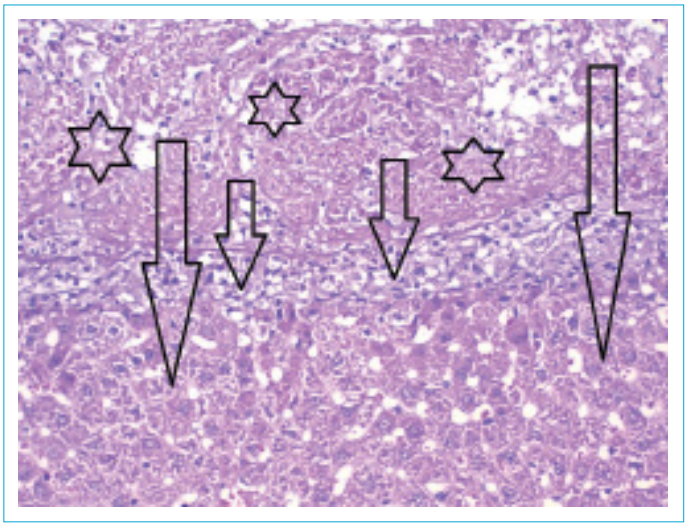

**Figure 4.** Histopathological appearance in liver treated with Algan Hemostatic Agent (AHA) liquid a week after procedure, Star: Early organized image forming barrier of AHA gel form on the surface of the liver lobectomy incision line, Short arrow: Macrophages accumulating between the parenchyma of the liver and the AHA barrier, Long arrow: After 7 days of administration of AHA liquid form, normal liver image without necrosis and inflammation (hematoxylin and eosin stain ×200).

groups and control in terms of necrosis and inflammation ($p>0.05$).

## Discussion

In this study, three different forms of AHA were tested as local hemostatic agents and all of them completely controlled the bleeding of liver laceration in a very short time compared to the control, and the results were found to be highly significant. Although the powder form controlled the bleeding more rapidly, no statistical difference was observed between the gel form and the bleeding control efficacy between them. However, the difference between the powder form and the liquid form was found to be statistically significant. There was no statistical difference between powder form and liquid form. Results for three different forms of AHA are shorter than all other local hemostats used for this purpose in the world.

Three laceration models[13] were created by introducing a total of three iatrogenic lacerations in the anterior surface of the liver 1 cm in length and 2 mm in depth, which have been used synonymously in an experiment in the literature characterized by liver lobectomy or partial resection.[21]

In studies conducted in the literature, the mean duration of bleeding in the control group varies according to the studies. In Sprague Dawley rats, this time was found to be 223 s[22] and 377 s.[23] In our study, this time was 180 s in the non-heparinize control group and 380 s in the heparinize control group. Due to the many factors such as animal weight, the experience of the practitioner, technical differences, and laboratory conditions it is necessary to compare other with other products in the same study to evaluate bleeding control activity. In literature conducted in a similar study, surgical controlled at 47 s while Ankaferd Blood Stopper controlled the bleeding at 23 s.[23] In one study, the efficacy of surgical and Ankaferd Blood Stopper in the liver laceration model was investigated. In this study, the duration of post-trauma life with Ankaferd was 28.46 min and 28.89 min with surgical.[21] Another study examined the efficacy of fibrin glue and Ankaferd in liver laceration bleeding model. In this study, Ankaferd was able to control bleeding at 17 s and fibrin glue bleeding at 18 s.[13] In our study, there was no post-traumatic death, and bleeding stopped at 2 s.

Since the effectiveness of a hemostatic agent is closer to humans in the literature, it has been tried to be shown in larger animals, especially pigs.[24, 25]

According to the results of the present study, although the AHA is the most effective hemostatic agent used for this purpose in the liver laceration in the literature, the actual difference can only be demonstrated by comparative studies. This situation will be clearer with future work.

The AHA forms applied to the liver have not been adversely affected on liver healing. There were no differences in term of inflammation and cell necrosis according to the control.

In the literature, some studies have tried to show the amount of blood lost using blood drying papers instead of bleeding time.[21]

It is thought that this method is not a suitable method in liver laceration models because it is not possible to hold the applied gel, powder, and liquid in this regions. Bleeding duration was considered as a more definitive method, and this method was applied in our study. There is a need to liberate the literacy from the complexity of the concept and to standardize bleeding models.

## Conclusion

In this study, histological examination has shown that the AHA's hemostasis mechanism is physical. Accordingly, when AHA is applied to the liver laceration surface, it becomes a gel and forms a barrier by surrounding the fibrin, blood and blood components in the environment. This study has shown that the AHA is a highly promising product for hemostatic control in humans as a hemostatic agent.

As a result, AHA, a new herbal hemostatic agent, was found to be effective in stopping local bleeding in these experiments. However, more comparative studies are needed in this regard.

**Disclosures**

**Ethics Committee Approval:** For this study, approval was obtained from Kırıkkale University Animal Experiments Local Ethics Committee (Decision no. 2018/05).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – A.M., A.K., H..E, S.K.; Design – A.M., A.K., H.E., S.K.; Supervision – M.T., H.E.O.; Materials – A.M., A.K., H.E., S.K.; Data collection &/or processing – A.M., A.K., H.E., F.B., K.K.; Analysis and/or interpretation – A.M., A.K., H.E., F.B., K.K.; Literature search – A.M., A.K., H.E., F.B., K.K.; Writing – A.M., A.K., H.E., F.B., K.K.; Critical review – H.E.O.

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