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Investigation of clinical efficacy and safety of a new herbal "Algan Hemostatic Agent™" in lumbar disc herniation operations

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ABSTRACT

Aim. ALGAN Hemostatic Agent (AHA) is obtained with a standard mixture of 6 different herbs. It is a polysaccharide based hemostatic agent. The purpose of this study is to determine the clinical efficacy and reliability of AHA as a local hemostatic agent in lumbar disc herniation operations. *Materials and Methods*. In the study, the hemostatic efficacy of the product was observed on 28 volunteers underwent lumbar disc herniation surgery. In the treatment and control groups (14 patients each), operation times, bleeding stop times, pre- and postoperative hematocrit values (amount of blood loss), duration of hospital stay, and need for cautery use were compared. Traditional methods (cautery, ligation, etc.), which are used as a hemostatic in the operation, were always ready to be used effectively. The AHA application took 120 seconds. *Results*. While there was no difference between the groups in terms of preoperative hemoglobin and hematocrit values, postoperative hemoglobin and hematocrit values were statistically significant (p=0.033, 0.043). The amount of cautery use decreased significantly in the treatment group and the result was found to be statistically significant (p=.0.001). There was no significant difference in blood transfusion and mean operation times. *Conclusions*. AHA has been shown to be both effective in controlling bleeding and safe, so it can be used as an auxiliary product in capillary bleeding control in lumbar disc operations.

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Introduction

The ability to stop bleeding in surgical operations or other emergencies is very important in terms of preventing negative outcomes by reducing blood loss. For this reason, hemostatic agents are increasingly used to stop minor and major bleeding after injuries, traumatic cuts, dental operations, and surgical interventions. Lumbar disc herniation operations are among the top operations with a high risk of bleeding. An important cause of bleeding in lumbar disc herniation operations is intraspinal venous plexus rupture [1-3]. Since the intraspinal venous plexus wall is thinner than normal, it can easily rupture due to decompression during surgery. In some patients, bleeding control is difficult due to many factors. Therefore, a fast and effective hemostatic method is needed in posterior lumbar surgery. Currently, many hemostatic products with various forms developed for use in different bleeding indications are used in medical applications [4-6]. However, some of them are very expensive, inadequate or damaging to tissues. In addition, it may cause some complications such as cauda equina syndrome in the applied area [7]. In addition to hemostasis, these products also shorten the duration of hospital stay, depending on the technique applied [8]. Despite the many different products developed, a product that provides optimum bleeding control could not be produced. Therefore, it is important to develop a natural, effective, harmless, and very economical hemostatic product that can be used safely. The main purpose of this study is the investigation of the clinical efficacy and safety of the hemostatic product called Algan Hemostatic Agent™ (AHA). AHA has a full quality assurance certificate (1783-MDD-196) and EC design-examination certificate 1783-MDD-197). AHA is a 100% herbal polysaccharide-based product designed to help control bleeding during surgical procedures. The AHA does not contain animal or human components. AHA is a biocompatible, non-flammable, thin, dry, sterile, colorless liquid. AHA is water soluble, so there is no need for post-coagulation clearance from application sites.

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AHA is used in surgical interventions (excluding pediatric, eye and central nervous system interventions) as an auxiliary hemorrhage stopper when pressure, stitching, tying or other routine surgical bleeding cessation procedures are ineffective in the control of capillary, venous and arterial bleeding. It turns into a polymeric network in the area where it is applied, accelerates coagulation by trapping the blood in it, and thus creates a mechanical barrier in the area of the blood vessel where bleeding occurs [9-12].

Materials and Methods

Identity of the research product

AHA is a polysaccharide-rich product obtained from a standard blend of six different herbs without a single active ingredient (Figure 1). Plants where AHA is formed are: mistletoe, yarrow, grape leaf, blackberry leaf, walnut leaf, wolf claw (Table 1). As a result of the analysis, the rate of polysaccharide was found to be 57%. Phenolic substance content was found as 3.015 mg GAE/g gallic acid equivalent in 50 mg AHA sample. There are various sizes of tampons with liquid hemostatic agents.

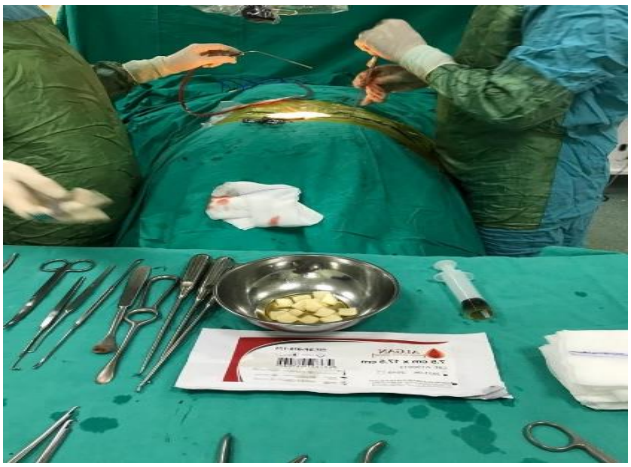

Figure 1. AHA is a polysaccharide-rich product obtained from a standard blend of six different herbs without a single active ingredient

Table 1. Algan hemostatic agent formulation

Plant name	Amount (gr)	Water	Infusion time (hour)	Bath temperature	Overall mix percentage
Blackberry leaf	100 gr	1 lt	48-49	50-60 °C	%8
Walnut leaf	70 gr	1 lt	48-49	50-60 °C	%10
Mistletoe, whole plant	100 gr	1 lt	48-49	50-60 °C	%35
Yarrow, above-ground part	120 gr	1 lt	24-25	50-60 °C	%25
Wolf claw, above-ground part	150 gr	1 lt	24-25	50-60 °C	%7
Grape leaf,	70 gr	1 lt	48-49	50-60 °C	%15

Ethical approval

The study was approved by the Clinical Research Ethics Committee. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Informed consent was obtained from patients who were admitted to the clinic after the operation decision was made before the operation.

Study Design

A total of 28 volunteers, who had lumbar disc herniation surgery and met the inclusion criteria, were included in this clinical study. This is a prospective study and patients were randomly assigned to the treatment and control groups. In this study, AHA was used as an aid in routine hemostatic applications such as ligation, however only the effect and reliability of AHA was monitored. All patients participating in the study have been comprehensively insured.

In case of bleeding during the operation, an AHA fluid soaked sponge was used as a bleeding stopper. Traditional methods (cautery, ligation, etc.), which are used as a hemostatic in the operation, were always ready to be used effectively. In the study, the hemostatic efficacy of the product was observed by lightly compressing the bleeding area with an AHA liquid-soaked sponge (Figure 2). This application lasted for 120 seconds. In case of continued bleeding at the end of the procedure or if there was bleeding from the edge of the sponge despite the compression, other routine methods were used for bleeding control without delay. In major bleeding that may pose a danger to the patient, it was planned to control the bleeding with other routine methods. The product was applied to patients only in case of bleeding during the operation. The primary endpoint of the study was that it was found to be statistically significant in controlling bleeding after 120 seconds of application, and that there were no complications related to postoperative AHA use.

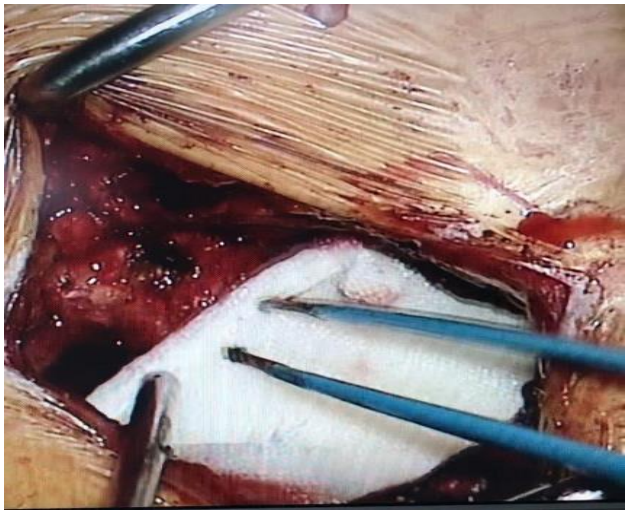

Figure 2. The hemostatic efficacy of the product was observed by lightly compressing the bleeding area with an AHA liquid-soaked sponge

Parameters evaluated

In the treatment and control groups, operation times, bleeding stop times, pre- and postoperative hematocrit values (amount of blood loss), duration of hospital stay, and need for cautery use were compared.

Working Population Selection

Inclusion criteria. The inclusion criteria of the volunteers for the study were determined as follows: 1) being between the ages of 50-75, 2) signing the volunteer consent form for research, 3) not having any hematologic disease.

Exclusion criteria. The criteria for not including volunteers in the research are: 1) not being between the ages of 50-75, 2) those with any hematologic disease, 3) not signing the voluntary consent form, 4) pregnant women, 5) breastfeeding mothers.

Method of assigning patients to treatment group

Among the patients who applied to the clinic for lumbar disc herniation, those who accepted to be in this adaptation and 14 patients who met the inclusion criteria constituted the study group. The control group consisted of 14 patients who were not included in the study and met the inclusion criteria in the same period. All surgeries were performed by the same surgeon. There was no recurrent operation in the treatment and control groups.

Dose selection in the study

Each patient received as many AHAs as needed. There is no specific dose selection.

Blinding

Since the control product was not used, it was not performed for this study.

Prior and concomitant therapy

The drugs used by the patients as anticoagulants were noted.

Statistical Methods and Determination of Sample Size

Power analysis was applied to determine at least how many patients the clinical study needed to be conducted. The evaluation was made as follows: $\alpha = 0.05$, $\beta = 0.20$, Test power = 0.80, Control group success rate = 0.20, Experimental group success rate = 0.70. In order for the study to be carried out under the conditions described above, at least 14 patients must be included in the groups. As the control group, 14 patients who operated in the clinic and did not use AHA in the same period were used. Comparisons between groups are one-way Wilcoxon Signed Ranks Test. Mann-Whitney test was used for comparisons between pairs.

Results

Demographic and other Key Features

When the treatment and control groups are compared, there are 10 men and 4 women in the treatment group. There are 4 males and 10 females in the control group. The mean age was 44 in the treatment group, while in the control group the mean age was 46. Results are presented in Tables 2, 3 and 4.

Table 2. Treatment group data

Patient No.	Age	Gender	Hospital (days)	Hematocrit value		Hemoglobin value		Number of cautery uses	Operation time (min)	Blood transfusion / Unit	AHA usage count
				Preop.	Postop.	Preop.	Postop.				
1	58	F	4	35.2	31.6	11.7	10.4	18	60	0	5
2	34	F	2	32.8	32.5	10.4	10.1	10	105	0	4
3	62	M	3	38.4	32.2	13.3	10.6	7	60	0	2
4	37	M	3	46.3	42.4	15.4	14.4	34	60	0	2
5	65	M	2	45	43.1	15.5	14.5	17	60	2	5
6	41	M	2	46.9	43.2	15.6	14.1	9	90	0	7
7	49	F	3	50.2	45.4	16.8	15.1	12	60	0	4
8	45	M	2	44.1	39.2	14.7	13.7	14	75	0	5
9	48	M	1	40	39.4	13.7	13.4	14	60	0	5
10	33	M	3	45.6	39.8	15.1	13.9	12	60	0	4
11	43	M	4	42.5	41.6	14.5	14.1	17	60	0	5
12	44	M	2	44.5	44.4	15.2	15.1	12	60	0	6
13	19	M	2	43.3	42	14.9	13.8	11	60	0	5
14	38	F	2	39.5	34	13.4	12.1	7	60	0	2
Average	44 ± 12,22	10M/4F	2.5 ± 0.85	42.45 ± 4.76	39.34 ± 4.79	14.30 ± 1.68	13.24 ± 1.72	13.86 ± 6.75	66.43 ± 14.06	0.14 ± 0.53	4.36 ± 1.49

Table 3. Control group data

Patient No.	Age	Gender	Hospital (days)	Hematocrit value		Hemoglobin value		Number of cautery uses	Operation time (min)	Blood transfusion / Unit	AHA usage count
				Preop.	Postop.	Preop.	Postop.				
1	53	F	2	41	33.8	13.4	11.3	20	60	0	0
2	44	M	2	49.8	45.7	16.4	15.3	23	60	0	0
3	42	F	2	34.1	25.4	11.4	8.5	25	60	2	0
4	55	M	2	41.1	35.9	13.7	12.1	22	60	0	0
5	31	M	2	40.8	35.3	13.1	11.1	20	60	0	0
6	68	F	2	37.2	30.2	12.1	10.3	18	90	0	0
7	30	F	3	35	32.8	12.1	10.7	24	90	0	0
8	28	F	2	41.8	37.5	13.7	12.4	18	80	0	0
9	30	M	2	45	40.3	15.3	13.3	33	60	0	0
10	37	F	2	38	28.7	12.7	9.4	36	60	2	0
11	31	F	3	36.5	23.8	12.2	8.2	27	80	0	0
12	64	F	2	38.1	33.3	13.1	11.4	33	90	0	0
13	71	F	2	38.8	34.1	12.3	11.7	38	90	0	0
14	60	M	1	48.7	41.7	16.4	14.3	26	90	0	0
Average	46 ± 15,55	4M/10F	2.07 ± 0.47	40.42 ± 4.71	34.18 ± 6.04	13.42 ± 1.58	11.43 ± 2.02	25.93 ± 6.63	73.57 ± 14.46	0.29 ± 0.72	0±0

Table 4. Comparison of the mean values of the groups

	Age	Gender	Hospital (days)	Hematocrit value		Hemoglobin value		Number of cautery uses	Operation time (min)	Blood transfusion / Unit	AHA usage count
				Preop.	Postop.	Preop.	Postop.				
Treatment group data	44 ± 12,22	10M/4F	2.50 ± 0.85	42.45 ± 4.76	39.34 ± 4.79	14.30 ± 1.68	13.24 ± 1.72	13.86 ± 6.75	66.43 ± 14.06	0.14 ± 0.53	4.36 ± 1.49
Control group data	46 ± 15,55	4M/10F	2.07 ± 0.47	40.42 ± 4.71	34.18 ± 6.04	13.42 ± 1.58	11.43 ± 2.02	25.93 ± 6.63	73.57 ± 14.46	0.29 ± 0.72	0 ± 0

The mean hematocrit values before the operation were found as 42.45 in the treatment group and 40.42 in the control group ($p = 0.175$). The mean hematocrit values after the operation were 40.42 in the treatment group and 34.18 in the control group ($p = 0.043$). The mean preoperative hemoglobin values were 14.3 in the treatment group and 13.4 in the control group ($p = 0.1139$). The mean hemoglobin values after the operation were 13.2 in the treatment group and 11.43 in the control group ($p = 0.033$).

The average amount of cautery use was 13.9 in the treatment group and 25.9 in the control group. The result was statistically significant ($p = 0.001$). A total of 4 units of blood were transfused to one patient in the blood transfusion / unit therapy group and two patients in the control group. Average operation times were 66.4 minutes in the treatment group and 73.6 minutes in the control group. The comparison of the control and treatment groups is given in Table 5.

The results of the comparison of preop. and postop. hematocrit and hemoglobin in the control and treatment groups are given in Table 6. There was no difference in wound healing sites in the AHA group. Follow-up and treatment compliance was evaluated by the surgeon who conducted the research. No adherence to treatment was observed in any of the participants. AHA use did not cause serious side effects such as death or disability. In addition, AHA did not cause undesirable side effects such as local tissue damage, temperature increase, nor any vascular occlusion causing normal circulation deterioration. In all cases where AHA was applied, it was successful in controlling bleeding within 2 minutes. The primary endpoint of this study was determined as demonstrating the efficacy and safety in 14 patients who were administered the application, and this goal was achieved at the end of the study. The AHA was found to be effective and safe as a result of this clinical trial.

Table 5. Comparison of control and treatment groups

	Treatment Group (n = 14)		Control Group (n = 14)		P *
	Mean	Std. Deviation	Mean	Std. Deviation	
Age	44.00	12.22	46.00	15.55	0.190
Hospitalisation (days)	2.07	0.47	2.50	0.85	0.131
Preop hematocrit value	42.45	4.76	40.42	4.71	0.175
Post op hematocrit value	39.34	4.79	34.18	6.04	**0.043**
Preop hemoglobin value	14.30	1.68	13.42	1.58	0.113
Post op hemoglobin value	13.42	1.72	11.43	2.02	**0.033**
Operation time (min)	66.43	14.06	73.57	14.46	0.145
Number of cautery uses	13.86	6.75	25.93	6.63	**0.001**
Blood transfusion / Unit	0.14	0.53	0.29	0.72	0.152

* Mann-Whitney Test

Table 6. Comparison of preop. and postop. in control and treatment groups

		Hematocrit, preop.	Hematocrit, postop.	P*	Hemoglobin, preop.	Hemoglobin, postop.	P*
Treatment Group (n = 14)	Mean	42.45	39.5	0.001	14.2	13.3	0.007
	Std. Deviation	3.0	2.9		1.6	1.8	
Control Group (n = 14)	Mean	40.5	34.5	0.001	13.3	12.0	0.001
	Std. Deviation	3.4	2.5		1.7	1.9	

* Wilcoxon Signed Ranks Test

Discussion

In cases where compression, ligation, or cauterization is not performed on the vessel in major bleeding, bleeding control cannot be easily achieved with existing hemostatic agents. Therefore, whichever hemostatic agent is used, it is used as an aid to traditional methods. It is a product produced to help hemostasis in AHA. It has many advantages such as being ready to use, easy to use, and cheap. In the current study, AHA was found to be quite effective in achieving hemostasis compared to the control group. The control and treatment groups were compared and a statistically significant difference was found between the preoperative hematocrit and hemoglobin values, the difference in hematocrit values before and after the operation, and the postoperative values and the number of cautery use in the control group.

Some products such as microporous polysaccharide hemospheres and flowable hemostatic matrix, which are known as common and effective products in the market, are far from practical to use. They are not ready-to-use products and must be prepared during the operation. Products that do not need to be prepared and used are thrown away. Because they are expensive products, they create costs for patients. It is not practical to use expensive hemostatic agents in operations such as lumbar disc herniation fixation or in operations where the use of hemostatic agents in the patient cannot be predicted. Therefore, there is a need for easy-to-apply, ready-to-use cheap products. AHA is a ready-to-use product and can be used as needed. Unused products can be stored for use in other operations. Hemostasis is easily achieved by lightly compressing the AHA-soaked sponge in any bleeding area. Spreading of the liquid over a wide surface in the application area provides convenience in application.

The intraspinal venous plexus, also known as the Batson's venous plexus, is part of the vertebral venous system and consists of many small, valved, venous structures [1]. These veins surround the ventral and dorsal side of the dural sac and then join at the intervertebral foramen to form the extramedullary venous plexus. When the intervertebral disc is herniated and the vertebral canal is narrow, the Batson's venous plexus in the spinal canal becomes compressed and causes venous irritation. It is inevitable to touch or cut these vessels during the operation and bleeding is difficult to control. The hemostasis method commonly used in these operations is bipolar electrocoagulation. On the one hand, its effect on the venous plexus is limited in bleeding control, and on the other hand, there is a risk of damaging the peripheral nerves by generating local heat [1]. Currently, the main hemostatic method for intervertebral venous plexus

bleeding is gelatin sponge filling. However, too much gel foam can cause nerve and nerve root compression of the spinal cord [13].

Absorbable hemostatic products are widely used in various surgical operations to assist with hemostasis [3-5,14]. AHA is an easily absorbable product in liquid form that provides local hemostasis, which is not used as a filler. While it provides hemostasis in the area where it is applied, it does not create a mass effect by accumulating and does not need to be cleaned from the area. It contributes to hemostasis by easily spreading all over the area where it is applied.

The hemostatic technique used has an effect on the duration of hospital stay [8]. Although AHA reduced the duration of hospital stay, this was not statistically significant. It is important that hemostatic agents have an effect on regional healing and thus increase and decrease the occurrence of pain due to fibrosis.

Many products can cause fibrosis in the spinal area and have a neurotoxic effect [15]. Fibrosis is one of the most important complications of lumbar disc operations. For this purpose, studies are carried out on products that reduce fibrosis [16].

In a study, it was shown that polysaccharide-based hemostatic agents did not increase fibrosis in rats after laminectomy compared to the control group [17]. The effect of AHA on fibrosis in lumbar surgery has not been investigated in rats. However, it has been shown that there is a decrease in abdominal adhesion after splenectomy compared to the control group [9]. Although there is no increase in pain due to postoperative fibrosis in the current clinical study, it is not correct to comment that AHA does not cause fibrosis in the area where it is applied. Detailed radiological evaluation of human studies to be carried out on this subject is required after the operation.

In another study, histopathological effects of 9 different hemostatic agents were examined in the laminectomy model in rats. Nine different hemostatic agents were applied to the laminectomy area. After a period of 12 weeks, agar and bovine factor proteins, gelatin granules with thrombin, and gelatin paste, which had the lowest rate of chronic inflammation and fibrosis, were found. Fibrin sealant, absorbable collagen, oxidized cellulose polymer groups and powder hemostatic agents have been shown to increase fibrosis. Chronic inflammation has been found to be more in the herbal hemostatic agent [18]. AHA is also a herbal product and has been shown to reduce intra-abdominal adhesion after splenectomy in previous animal experiments. No fibrosis complications were observed in postoperative controls of these cases. In another study, polysaccharide hemostat, oxidized regenerated cellulose was shown to reduce epidural fibrosis compared to the control group [19].

Limitations of the study

Hemostasis is a physiological process affected by several local factors as well as other factors such as the patient's condition, the diameter and number of vessels damaged, and the amount of bleeding varies widely among patients. Therefore, it is not possible to obtain a standard result. In addition, the number of patients could have been made with the least number allowed by the statistical study due to ethical reasons.

Since this study is an efficacy and safety study, no comparison has been made with another product. In this study, randomization was not performed because no comparison product was used and there was no superiority study.

For this reason, comparative clinical studies are needed to show efficiency compared to other products used in the market.

As a result, in the control and treatment groups preop. and postop. were compared separately, and a statistically significant difference was found between hematocrit and hemoglobin values. Hematocrit and hemoglobin values were decreased in both groups. There was a difference between the groups in terms of the average amount of reduction, and the decrease was more pronounced in the control group.

This study is the first clinical study to demonstrate the efficacy and safety of AHA and is required for certification. Since it is the first study conducted in the clinic, the number of participants has been kept as low as statistics allow. Choosing the surgery with less bleeding is one of the limitations of the study. But this study was planned to demonstrate the safety rather than the effectiveness of AHA. For this reason, lumbar disc herniation surgeries were chosen in which bleeding is not expected during the operation.

Conclusions

Algan hemostatic agent's efficacy and reliability study in lumbar disc operations showed that AHA has been found to be effective in controlling bleeding and reducing blood loss in lumbar disc operations. AHA also significantly reduces the number of cautery use. In addition, it was found to be reliable since no complications developed.

This is an efficacy and safety study and has not been compared with another product. However, it would be appropriate to demonstrate the real effectiveness of AHA by conducting superiority studies with more participants with other different products available in the market.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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