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Research article

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Evaluation of ultrasonic intravascular thrombectomy system on a rabbit model in the treatment of deep vein thrombosis

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Ethics Committee Approval
The study was initiated after approval was granted by Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision numbered 65202830-050.04.04-319. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Advanced treatment options are needed in deep venous thrombosis (DVT), which is a special subgroup of venous disease. We examined this subgroup on an animal model and aimed to evaluate the effects of the ultrasonic intravascular thrombectomy system on vascular endothelial damage.
Methods: A total of 24 rabbits in 3 groups were used in the study. DVT was created in the common iliac vein by the administration of intravascular fibrin. One hour passed for DVT formation. The ultrasonic intravascular thrombectomy system and the mechanical thrombectomy system were used separately in the DVT groups. After one hour, samples obtained from the groups were examined histologically.
Results: Significantly less endothelial damage was detected in the ultrasonic intravascular thrombectomy system group compared to the mechanical thrombectomy group ($P<0.05$).
Conclusions: Ultrasonic intravascular thrombectomy method minimizes the thrombus load and causes minimal endothelial damage. These findings show that the ultrasonic intravascular thrombectomy method can be used successfully in DVT treatment.

Keywords: Deep vein thrombosis, Ultrasonic intravascular thrombectomy system, Animal model, Endothelial injury

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Introduction

Deep venous thrombosis (DVT) has a wide range of symptoms. If asymptomatic, it is defined as subclinical DVT. It may cause mortality due to a pulmonary embolism. Venous ulcer and postphlebitic syndrome may occur in untreated patients. Cancer, postoperative long-term bed dependency, sedentary lifestyle, advanced age, obesity, tobacco use, organ failure, neurological diseases, hereditary causes, increased platelet count, and increased red blood cell distribution width may have a predisposing effect [1, 2]. In the Caucasian race, which includes Turkey, DVT cases are observed at a rate of 50-124/100,000 per year [3]. Innovations are needed in the prevention, diagnosis, follow-up, and treatment of DVT because it is a very common disease with high morbidity and mortality due to venous thromboembolism [4]. There are many treatment methods of DVT, including interventional techniques. However, no studies are comparing these methods with each other in terms of vascular endothelial damage. The absence of endothelial damage is essential for the effectiveness of the treatment and prevention of recurrence. In this study, a comparison was made between mechanical thrombectomy and the ultrasonic intravascular thrombectomy system in terms of endothelial damage.

Materials and methods

The study was initiated after the approval was granted by Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision numbered 65202830-050.04.04-319. The study was conducted on a total of three groups and twenty-four rabbits. There were eight rabbits in each group (New Zealand white rabbits, 6-8 months old, males weighing 3.2-3.5 kg, females weighing 2.75-3 kg). The rabbits were housed in equally sized cages and at a constant temperature of twenty degrees, in a laboratory environment capable of receiving twelve hours of the night and twelve hours of daylight. Standard rabbit food was used in all rabbits and their water was changed every other day. 90 mg/kg subcutaneous ketamine and 3 mg/kg intraperitoneal xylazine were administered to the animals for anesthesia before surgical applications.

Group 1: No procedures were performed on the animals in this group. At the end of the experiment, iliac vein samples were obtained after sacrification.

Group 2: DVT was created in the iliac vein and a mechanical thrombectomy was performed. At the end of the experiment, iliac vein samples were obtained after sacrification.

Group 3: DVT was created in the iliac vein and thrombectomy was performed with the ultrasonic intravascular thrombectomy system. At the end of the experiment, iliac vein samples were obtained after sacrification.

Acute DVT was induced in each study group by catheter-mediated fibrin application previously described by Itoh et al. [5]. The common iliac vein was thrombosed with a fibrin-coated catheter of 0.9 mm in diameter. In the study of Itoh et al., thrombosis was observed to start approximately within 2 minutes after fibrin administration and reached the desired level at the 20^{th} minute. Therefore, thrombectomy began 1 hour after thrombosis developed. Surgical procedures were performed under general anesthesia and per the ethical rules. The iliac veins of the animals were explored and a thrombectomy was performed so that both the thrombectomy catheters were visible and manually felt. A mechanical thrombectomy catheter (Fogarty catheter) and an ultrasonic intravascular thrombectomy system catheter (Mavera Medical Devices Inc.) were used for thrombectomy. The samples removed after the animals were sacrificed were evaluated histopathologically and comparisons were made separately for each group.

Histopathological method

The common iliac vein tissues were fixed in 10% neutral formalin solution and embedded in paraffin blocks after routine alcohol-xylol procedure. The 5 µ sections on the polylysine slides were stained with hematoxylin-eosin, the size of the thrombotic mass was evaluated under a light microscope, and the damage to the endothelium was evaluated as shown in the table (Table 1).

Table 1: Histopathological scoring system of endothelial damage

Histopathological Score	
Thrombus in the entire lumen (3)	Damage to the entire endothelium (3)
Thrombus in half of the lumen (2)	Damage to half of the endothelium (2)
Thrombus in a quarter of the lumen (1)	Damage to the quarter of the endothelium (1)
No thrombus (0)	No damage (0)

Statistical analysis

The data were analyzed with the SPSS 20.00 program (StataCorp LP, College Station, TX, USA). The difference between the groups was determined by the Kruskal Wallis test, one of the nonparametric tests, and the differing group was assessed with the Mann Whitney U test. A *P*-value of <0.05 was considered statistically significant.

Results

Statistically significant differences were found between the groups in terms of both thrombosis and endothelial damage in the common iliac veins (Table 2).

Table 2: Statistical comparison of groups according to results

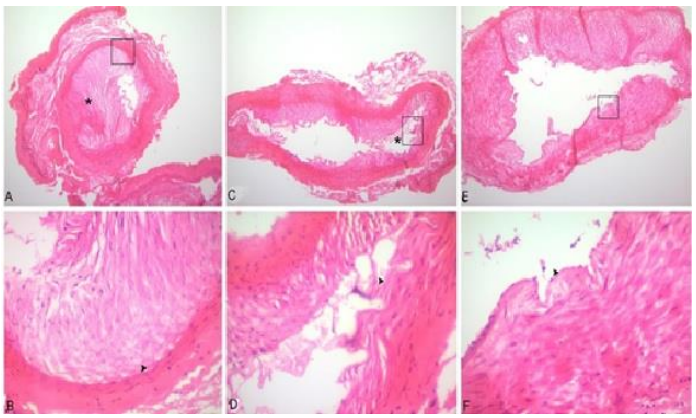
Groups	Thrombosis	Endothelial Damage
Group 1 (Control group)	0.16(0.40)c	1.33(0.51)b
Group 2 (Mechanical thrombectomy group)	2.16(0.40)a	2.16(0.40)a
Group 3 (Ultrasonic intravascular thrombectomy system group)	1.16(0.40)b	2.16(0.40)a
Statistical Significance (*P*-value)	<0.05	<0.05

Table 3: Differences between the groups in terms of endothelial damage in the post-hoc Dunn test (Std: Standard)

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	*P*-value
Ultrasonic intravascular thrombectomy system vs. the control group	1.063	4.464	0.238	0.812
Mechanical thrombectomy vs. the control group	-18.937	4.464	-4.242	0.000
Ultrasonic intravascular thrombectomy system vs. mechanical thrombectomy	-20.000	4.464	-4.480	0.000

The lumen of the iliac vein was completely covered with a thrombotic mass in the mechanical thrombectomy group, and leukocyte infiltration was observed in the thrombotic mass. The ultrasonic thrombectomy group had a mild thrombotic mass and mild leukocyte infiltration, while no thrombotic mass was found in the control group. In the ultrasonic thrombectomy group, the vascular endothelial structure had a normal histological appearance, whereas in the mechanical thrombectomy group, moderate degeneration and desquamation were observed in the vascular endothelial cells. There was no endothelial injury in the control group ($P<0.001$) (Figure 1) (Table 3).

Figure 1: Common iliac vein sections stained with hematoxylin-eosin, light microscope images showing thrombotic masses and endothelial damage



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Discussion

Although venous thrombosis can be seen in any vein, lower extremity DVTs cause life-threatening complications such as pulmonary thromboembolism and postphlebitic syndrome more often. DVT, seen at a rate of 1% in older ages, is most common in the lower extremities and pelvic veins [6]. The postphlebitic syndrome is seen in 5-10% of the lower extremity DVT patients [7].

Symptoms begin to appear in most patients shortly after thrombosis develops. The first 2 weeks are considered acute DVT, 2-4 weeks, subacute DVT, and >4 weeks, it is defined as chronic DVT. DVT treatment can also vary depending on the stage of the disease. Medical, interventional, and surgical methods are used according to the stage of the disease. Commonly used interventional treatment methods include mechanical thrombectomy, aspiration thrombectomy, pharmacomechanical thrombectomy, and ultrasonic thrombectomy [8, 9].

Each of the methods used to prevent postphlebitic syndrome has a great advantage. All significantly reduce the development of postphlebitic syndrome as a result of vein recanalization [10-12]. These methods help not only to prevent changes in the chronic phase but also to eliminate complaints in the acute phase, reduce thrombus burden and shorten lysis time [13-15]. In addition, they reduce hospital costs by preventing long hospitalizations [16]. However, the use of significant amounts of fibrinolytic agents in pharmacomechanical methods increases the risk of bleeding [17].

Open surgical methods are still an option in the treatment of acute DVT. Studies are reporting that it has a reliability of close to 100% in preventing postphlebitic syndrome [18]. All the methods and techniques listed can be used alone or in combination [19, 20] in lower and upper extremity thrombosis [21].

This study compared conventional mechanical thrombectomy and ultrasonic thrombectomy methods on a rabbit DVT model in terms of thrombus load, presence of thrombus, and endothelial damage. Based on our results, ultrasonic thrombectomy was superior to conventional thrombectomy in clearing the thrombus and reducing the thrombus load as well as endothelial damage.

This study was designed to evaluate the early phase of acute deep vein thrombosis. In daily life, most patients clinically transform from acute deep vein thrombosis to chronic deep vein thrombosis. This shows that it is more effective to monitor long-term results. The most important outcome expected in the early period in the treatment of acute DVT is the reduction or complete elimination of the thrombus load. Therefore, the lower thrombus load in ultrasonic thrombectomy is an indication that the device has the desired feature. In addition, minimal endothelial damage in the ultrasonic thrombectomy group can be considered a positive sign of long-term results.

Limitations

There are several limitations to our study. First, only two of the thrombectomy methods were compared. The study being an animal experiment limited the chance of a long-term follow-up. In addition, clinical studies including long-term follow-ups are needed.

Conclusion

We observed that the ultrasonic thrombectomy method minimized early thrombus load and caused minimal endothelial damage. These findings suggest that the ultrasonic thrombectomy method can be successfully used in the treatment of acute deep vein thrombosis.

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