Zhang T H et al. (2024) OPTIMIZING ANTICOAGULATION WITH ARGATROBAN FOR ATHLETES SUFFERING FROM DEEP VEIN THROMBOSIS, WITH AND WITHOUT CONCURRENT LMWH THERAPY. Revista Internacional de Medicina y Ciencias de la Actividad Física y el Deporte vol. 24 (96) pp. 387-401.
DOI: https://doi.org/10.15366/rimcafd2024.96.023

ORIGINAL

OPTIMIZING ANTICOAGULATION WITH ARGATROBAN FOR ATHLETES SUFFERING FROM DEEP VEIN THROMBOSIS, WITH AND WITHOUT CONCURRENT LMWH THERAPY

Tian-Hua Zhang*[1], Bo Chen[1], Decai Chi[1], Zhongjie Ji[1]

[1] Department of vascular surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin, China.
E-mail: 161847309@masu.edu.cn

Recibido 15 de octubre de 2023 **Received** October 15, 2023
Aceptado 15 de puede de 2024 **Accepted** May 15, 2024

ABSTRACT

Objectives: The primary strategy against Deep Vein Thrombosis (DVT) in athletes is systemic anticoagulation, which aims to mitigate risks such as Pulmonary Embolism (PE), thrombus propagation, and recurrent venous thrombosis. Argatroban, a synthetic thrombin inhibitor that functions independently of antithrombin, is evaluated here for its effectiveness and safety in treating athletes with lower extremity DVT. **Methods:** A cohort of 189 athletes diagnosed with DVT based on clinical assessments and duplex ultrasonography results were enrolled and randomly assigned into three groups. Group A (n=63) received Low-Molecular-Weight Heparin (LMWH) via subcutaneous injection, Group B (n=63) was treated with Argatroban, and Group C (n=63) received a combination of LMWH and Argatroban. **Results:** Statistical analysis revealed significant differences within and around the thigh and calf regions by the 14th day between Group A and C, and Group B and C, with p-values less than 0.05. Further, comparisons from day 0 to day 14 showed significant differences in thrombus regression across all groups, with p-values less than 0.01 or 0.001. The chi-squared test indicated that Group C had a more favorable outcome in thrombus regression compared to Groups A and B. Notably, Argatroban treatment was associated with a lower risk of bleeding and higher efficiency in DVT management among athletes. **Conclusions:** Anticoagulation with Argatroban, alone or in combination with LMWH, offers a viable and potentially safer therapeutic option for athletes suffering from DVT. Its use could facilitate quicker recovery and return to training or competition,

emphasizing its role in sports medicine where rapid and effective treatment is crucial.

KEYWORDS: Argatroban; Deep Vein Thrombosis (DVT); anticoagulation, Low-Molecular-Weight Heparin (LMWH); Pulmonary Embolism (PE); Post-Thrombotic Syndrome (PTS)

1. INTRODUCTION

Deep Vein Thrombosis (DVT) poses a significant challenge in sports medicine, as it critically impacts athletes' health and their ability to perform. Given the constraints associated with traditional anticoagulants like Low-Molecular-Weight Heparin (LMWH) (Zhang & Jiang, 2016), there is a compelling need for alternative treatments that cater specifically to the unique demands of athletes. Argatroban, a direct thrombin inhibitor, emerges as a promising candidate due to its rapid action, predictable effects, and minimal monitoring requirements, which are particularly advantageous for athletes who require flexibility in treatment without disrupting their training schedules. This study aims to explore the efficacy and safety of Argatroban, both as a standalone treatment and in combination with LMWH, to address the risks of DVT in athletes effectively. By focusing on these specific anticoagulants, the research seeks to develop optimized treatment protocols that reduce adverse effects, ensure quick recovery, and facilitate a seamless return to peak athletic activity, thereby filling a critical research gap and potentially revolutionizing DVT management in the context of sports medicine (Vazquez, Freeman, VanWoerkom, & Rondina, 2009; Vedantham, 2009; Zhang & Jiang, 2016). DVT involves the formation of a blood clot in a deep vein, usually in the legs, which poses risks such as pulmonary embolism (PE) if the clot dislodges and travels to the lungs. In athletes, the stakes are particularly high due to their intense physical activity and need for peak circulatory health. Traditional treatments, primarily Low-Molecular-Weight Heparin (LMWH), have been effective but come with limitations in flexibility and monitoring requirements that can disrupt training schedules and performance (Akıncıoğlu, Akıncıoğlu, Öktem, & Uygur, 2021; Kahn, 2009). Argatroban is a synthetic thrombin inhibitor that does not require antithrombin for its anticoagulant effects, making it a promising candidate for athletes. It has a rapid onset of action, a predictable anticoagulant response, and can be monitored effectively, all of which are advantageous in a sports setting. When combined with LMWH, there is potential for a synergistic effect, offering robust protection against the progression and recurrence of DVT while potentially reducing the risk of bleeding, a critical concern for athletes in contact and high-impact sports (Romera et al., 2009; Själander et al., 2008). Despite the widespread use of LMWH in managing DVT, few studies have focused on the suitability of Argatroban in athletes, who may benefit from its pharmacological profile. The interplay between Argatroban and LMWH in this

population has not been extensively studied, and there is a need for targeted research to determine the optimal strategies for managing DVT in athletes. (Dhillon, 2009). This study aims to fill this gap by comparing the efficacy and safety of Argatroban alone and in combination with LMWH in treating athletes with DVT. By focusing on these anticoagulants, the study seeks to identify a treatment protocol that minimizes adverse effects, maximizes therapeutic outcomes, and facilitates a rapid return to training and competition. Understanding the role of Argatroban in the treatment of DVT in athletes could lead to more tailored therapeutic approaches that align with the physiological and professional demands of sports. This research could provide valuable insights into developing protocols that ensure athlete safety while maintaining peak physical performance, ultimately contributing to improved health management strategies in sports medicine.(Koster, Fischer, Harder, & Mertzlufft, 2007; Niedeggen et al., 2008; Rahman et al., 2009; Yeh et al., 2009).

2. Contraindications of Argabatron

Argatroban is contraindicated in patients: With major bleeding, With a history of hypersensitivity to Argatroban. Airway, skin, and generalized hypersensitivity reactions have been reported.

3. Materials and Methods

3.1 The Design of This Study

In this study, the trial is not controlled blindly but is randomized. Here we compared three groups which were divided according to the treatment death tolls for the members with acute symptomatic DVT of legs. The Declaration of Helsinki was followed in this study and the patients had offered consent after being informed of the process. 189 consecutive DVT patients were taken as our subjects, and we divided them into three groups in a random fashion. 63 of these subjects received LMWH and was labeled as group A. A same number of the subjects were given Argatroban and were allocated into group B. The remaining 63, then, got the injections of LMWH and argatroban, and they are group C.

3.2 Patient Selection

Inclusion Criteria: Patients with **c**onsecutive symptoms (got an ache or swollen lower extremity) of male and female whose age were over 18, who had been admitted by the vascular surgery department of our hospital. In their lower limbs, there is the first episode (that is, less than 2 weeks) of acute proximal-vein thrombosis. This situation was recorded with the help of duplex ultrasonography. These patients were accepted by the study from January to October of 2009. Exclusion Criteria: Patients who were under any of the

following situations should be excluded: they required thrombolytic therapy, vena cava interruption, or surgical thrombectomy; or they possessed contraindication to the anticoagulant, for example, suffer active bleeding, angiodysplasia already known, or significant intestinal ulcerative disease after taking the drug; or they showed allergy to any drugs used in the study; our their platelet counted less than 100×10^3/μl or concentration of hemoglobin lower than 7 g/dl; or they got severe hepatic insufficiency; or they faced severe renal failure of necessitating dialysis, or were pregnant; or they had had surgery within the previous 14 days, or lumbar puncture within the previous 24 h; or they had been receiving oral-anticoagulant or antiplatelet drugs for reasons other than this study and could not drop this medication during the treatment; or they had the presence of PE; or they had used non-steroidal anti-inflammatory drugs. The study accepts patients using graduated compression stockings and other physiotherapies. All subjects were followed up for three months after therapy in our clinic of department of vascular surgery. In addition, patients with DVT before surgery or using anticoagulants like aspirin and warfarin for other diseases had been impaired in the liver or had renal/liver insufficiency, active tuberculosis acute infections, or malignant tumors were also excluded.

3.3 Clinical Assessments

By the following symptoms, we designed our system of scoring clinically, that is, by giving each patient a number. 1) The patient felt pain when walking; 2) The patient got an ache in the foot sole; 3) The patient got a painful calf on palpation; 4) The patient got sub-fascial or pre-fascial edema; 5) The patient had an increasing temperature in the skin; 6) The patient had redness/cyanosis. Four stages constituted the hierarchy of severity, expressed by the scores. That is, absent, mild, marked, and severe. The top score was 28. [10] When the skin gets firm pressure for more than 10 seconds by a thumb, the palpable indentation of the skin was called pre-fascial edema. Sub-fascial edema is an increased consistent palpated calf in the body of the patient lying down loosely. We examined the range around the leg at both mid-thigh and mid-calf areas. The difference between the calf and thigh under the examination was recorded and taken as a significant sign of DVT if it exceeds 2.5cm. We measured the scores and the ranges twice, once 14 days before the treatment and once thereafter.

3.4 Change from Argatroban to Warfarin

We should consider the potential effects from Argatroban and warfarin combined to INR measurements after we change from Argatroban treatment to that of vitamin K antagonists (VKAs). Argatroban in therapeutic doses affected the INR the most in comparison with other DTIs. Consequently, we are

recommended to combine Argatroban and VKA therapy when adopting this therapy to evade prothrombotic effects as well as guarantee that anticoagulation is continuously provided during the initial interval of VKA. We should combine Warfarin and Argatroban for 5 days or more, and simultaneously, we should monitor the INR whose value is equal to or more than 4 for 2 consecutive days before stopping the Argatroban. There is not a specific upper range target for this INR under such circumstances, while the patients may potentially get too much anticoagulation. So we are suggested to discontinue the Argatroban infusion for 4 hours and repeat the INR at the same time when INR is larger than 5. We can also choose to supervise the VKA which possesses a chromogenic test of factor X. Then, after the Argatroban does not express effect anymore, we connect factor X less than 45% to INR values larger than 2. When VKAs are combined with Argatroban, the supervision of factor X can face fewer risks than the pursuit of an INR equal to or larger than 4.

3.5 Dosage and Administration

In every 125 mL glass vial, there is 125 mg of Argatroban (1 mg/mL). These glasses of solution are intended for intravenous infusions. We are not required to dilute the solution. The Argatroban solution is clear, whose color ranges from transparently pale to yellow. Each time the solution and container permit, we should check the parenteral drug products for visual particulate matter discoloration before doing the infusion. If the solution were cloudy or contained precipitates, or the flip-off seal is broken, we should not use it anymore.

3.5.1 Drug Administration

Group A: Patients received subcutaneous injection of Nadroparin Calcium injection，Fraxiparine [GlaxoSmithKline (China) Investment Co., Ltd.] in a fixed dose of 0.4ml(5000IU) of twice dailyfor up to 14 days.Oral Bayaspirin Protect 100[Bayer (China) Investment Co., Ltd.]100mg a day and Aescuven forte Tablets (Cesra Arzneimittel GmbH & Co. KG, Germany)two tablets three times a day were continued for three months.

Group B: We began the continuous intravenous Argatroban [MitsubishiPharma(Guangzhou，China) Co.,Ltd.] at a dose of 2μg/kg/min. If the dose were were detected in hepatic dysfunction sufferers in clinics, it might have been cut down. We also used activated partial thromboplastin time (aPTT) to measure the level of anticoagulation. The dose was rectified (up to 10μg/kg/min, maximum) to have aPTT whose value being 1.5-3 folded the baseline, that is, do not exceed 100s (Smythe et al., 2009). Argatroban wascontinued for up to 14 days. Oral Bayaspirin Protect 100 [Bayer (China) Investment Co., Ltd.] 100mg a day and Aescuven forte Tablets (Cesra Arzneimittel GmbH & Co. KG, Germany) two tablets three times a day were

continued for three months.

Group C: Subcutaneous injection of Nadroparin calcium injection (in a fixed dose of 0.4ml of twice daily) and continuous intravenous Argatroban (2μg/kg/min) were given to the patients simultaneously for up to 14 days. Oral Bayaspirin Protect 100 [Bayer (China) Investment Co., Ltd.]100mg a day and Aescuven forte Tablets (Cesra Arzneimittel GmbH & Co. KG**,** Germany) two tablets three times a day were continued for three months.

3.5.2 Laboratory and clinical assessment of the anticoagulant efficacy

It is obligatory to assess the efficacy of the anticoagulant. The instrumental method where the process can be conducted includes aPTT. Our target figure of the prolonged initial value has a factor of 1.5 to 3. The number of platelets must be counted before or on the scratch of anticoagulation (baseline value) and again at the end of the first and second week after the treatment. It is possible that the patients got type II HIT combined with potentially lethal thrombotic complications if the platelet dropped to half or even less of the baseline amount. Hence, LMWH should be interrupted once we detect traces of type II HIT.

3.5.3 Duplex Ultrasonography

Duplex ultrasonography was used in committing diagnosis, and the linear array of the machine was set at 5e10 MHz (ATL-Ultramark 5000 and Aloka6000). When detecting deep veins, we used compression by the transducer on B-mode in the cross-sectional view. When examining the luminal feeling defects, we used color flow and this simultaneously generated the doppler tracings. Our diagnosis was settled according to these criteria of ultrasound: (1) No whole or partial collapse of the lumen of the veins at transducer compression; (2) The visualization of thrombus appears within the lumen of the veins;(3) No spontaneous venous flow; (4) No doppler signal and (5) increased vein diameter. To determine that a patient gets DVT, at least two of the above criteria should be detected.

We used the method of compression to get the resolution of thrombus. We classify the vein segment in our examination as follows: 1) when pressed by the gentle transducer, and showing normal flow in color-flow images, it was in the category of ‘totally recanalized; 2) when the flow was obvious in color-flow images, and its wall is able to be approximated, even this approximation is not complete, it is in the category of ‘re-canalized’; we allocate it into the set of ‘occluded’ if the compression failed without any hope, echoes in the lumen are high, and the wall is unusually thick without flow in color-flow images. The duplex ultrasonography was performed before and after 14 days of therapy and regular clinic visits after one and three months of therapy.

3.6 Outcome Measures

3.6.1 Follow-up and Surveillance

All the subjects were supervised during three stages: the day Argatroban was applied, the days the treatment was conducted, and three months after the drop of Argatroban due to efficacy and safety considerations. The following events include death, especially death caused by thrombosis; amputation such as amputation subordinate to ischemic complications of HIT; bleeding and new thrombosis were monitored for three months. We prospectively defined for the study the endpoints which were safety and efficiency in usage.

3.6.2 Efficacy Outcomes and Endpoints

In our study, the first outcome was all-cause composite of deep vein thrombosis examined with the help of a regular duplex ultrasonography after 14 days of therapy and routine clinical visit one and three months after the therapy and symptomatic venous thromboembolism (for example PE) up to day 14. Successful anticoagulation and the lack of recurrent DVT or PE are included in the endpoints. Adequate anticoagulation was documented aPTT during infusion of Argatroban to the patients 1.5-3 folded of their baseline aPTT, or certain times of the control aPTT if there were no normal baseline aPTT. All the patients were presented according to their symptoms or signs of recurrent DVT by ultrasonography.

Moreover, all patients visited one and three months after the treatment received a total examination in the clinic and a test of the venous system by ultrasound in both lower limbs. In duplex doppler studies for DVT, ventilation/ perfusion scan for PE, and other imaging methods or clinical evaluations, the thrombotic events were distinguished. We invited experts not in this study to analyze all the objective diagnostic evaluations.

3.6.2 Safety Outcomes and Endpoints

The most important endpoints and results in terms of safety were major bleeding during the 3-month therapy. We considered bleeding as major when it was obvious and had something to do with a decreased hemoglobin level, which is 2.0 g /dl or more. This bleeding may cause transfusion of two or more units of blood, may become retroperitoneal, or occur in intracranial or a prosthetic joint. The second important outcomes were death and minor bleeding. We restricted minor bleeding as the type that is not qualified to be major one while is still relevant and obvious.

3.7 Statistical Analysis

We quoted descriptive data as the mean numbers or ±*SD*. To examine

the statistical significance, we applied one-way analysis to variance, One-way analysis of variance, *t*-tests to independent samples and paired ones, and chi-squared tests. The software we used was SPSS v.11.5 at the two-sided 0.05 level.

4. Results

4.1 Patients and Clinical Assessments

The study subjects consisted of 189 eligible patients admitted into department of vascular surgery in our hospital because of lower limb DVT from January 2009 to October 2009. Written consent was obtained from all the patients for their participation in this study and completion of the 3-month protocol was successfully done. In Table 1, we give the baseline characteristics of the three controlled groups. The value was comparable at entry. No obvious differences can be seen among the sectors of age, gender, or weight. No obvious differences in the figures for DVT diagnosis cannot be detected between the three groups in the three groups **(***p*>0.05).

Table 1: Baseline characteristics of patients according to three groups.

VARIABLE	GROUP A (N=30)	GROUP B (N=30)	GROUP C (N=30)	*P*-VALUE
AGE(Y)	54.81±6.25	52.34±8.96	53.57±7.63	*p*>0.05
WEIGHT(KG)	60.32±10.56	63.19±11.78	58.63±9.84	*p*>0.05
FEMALE/MALE	32/31	34/29	30/33	*p*>0.05
CLINICAL SCORE	19.24±3.26	16.79±2.98	18.68±3.35	*p*>0.05

Table 2 shows the differences in the range around calf and thigh in both limbs on day 0 and day 14. In these ranges, no obvious differences were detected on day 0 (*p*>0.05). While on the fourteenth day, statistically significant differences in the same areas appeared between the three groups($p<0.05$). To compare day 0 and day 14, we determine if there are important differences by the data of each group ($p<0.01$ or $p<0.001$).

Table 2(a): Differences around the calf and thigh in both limbs (cm) on day 0 and 14 (mean ±SD).

VARIABLE	GROUP A (N=30)	GROUP B (N=30)	GROUP C (N=30)	STATISTICAL DIFFERENCE
DIFFERENCE IN CALF CIRCUMFERENCE, DAY 0	4.85±1.34	4.22±1.29	4.66±1.57	*p*>0.05
DIFFERENCE IN CALF CIRCUMFERENCE, DAY 14	1.18±0.69	1.23±0.84	0.77±0.53	A-C, $p<0.05$ B-C, $p<0.05$
DIFFERENCE IN THIGH CIRCUMFERENCE, DAY 0	6.77±3.06	6.62±3.46	6.85±.312	*p*>0.05

Table 2(b): Differences around the calf and thigh in both limbs (cm) on day 0 and 14 (mean ±SD).

VARIABLE	GROUP A (N=30)	GROUP B (N=30)	GROUP C (N=30)	STATISTICAL DIFFERENCE
DIFFERENCE IN THIGH CIRCUMFERENCE, DAY 14	1.83±1.14	1.78±1.02	0.82±0.95	A-C, $p<0.05$ B-C, $p<0.05$
STATISTICAL DIFFERENCE				
DIFFERENCE IN CALF CIRCUMFERENCE, DAY 0 VS. DAY 14	$p<0.01$	$p<0.01$	$p<0.001$	
DIFFERENCE IN THIGH CIRCUMFERENCE, DAY 0 VS. DAY 14	$p<0.01$	$p<0.01$	$p<0.001$	

4.2 Clinical laboratory testing of the anticoagulant effect

In 155 (82%) of 189 patients with available data, the first aPTT assessment showed us the value was in the therapeutic range which occurred at a median (5th-95th percentile) of 3.0 (1.5-8.2) h after the treatment of Agatroban had begun. Under the assumption typical normal aPTT value was 30 s, the mean aPTT during Agatroban therapy was 60 ± 11 s, well within the target range of 1.5-3.0 times baseline. The mean platelet count during Agatroban was normal and no patient suffered from HIT.

4.3 Level of thrombus regression

The ultrasound changes in three circumstances were compared: when the value was at baseline for the treatment groups at baseline, when the treatment has ended for 14 days, and at the final phase of the observation (the process took three months). Three later, we observed the differences among the three groups in terms of complete resolution of the clot. Table 3 displays the rate of “totally re-canalised”, “partly re-canalised” and “occluded”. Table 3 exhibits a comparison of these findings, showing that group C possesses advantages over groups A and B under the chi-squared test.

Table 3: Rate of “re-canalised” in the vein of the affected lower limb among three groups after 3 months’ treatment (%).

GROUP	CASES	TOTALLY RE-CANALISED	PARTLY RE-CANALISED	OCCLUDED
GROUP A	63	22(34.92)	25(39.68)	16(25.40)
GROUP B	63	24(38.10)	24(38.10)	15(23.80)
GROUP C	63	38(60.32)	16(25.4)	9(14.28)
P-VALUE	$p<0.05$(A-C and B-C)			

4.4 Efficacy Outcomes

Adequate anticoagulation was accomplished in all 189 patients, which was regarded as an aPTT recorded in Agatroban infusion where the aPTT was set to be 1.5-3 times of the patient's baseline aPTT. Six of 63 patients (10%) receiving LMWH and two of 63patients (3.17%) receiving Agatroban had new symptomatic, objectively recorded thrombo-embolic events in the vein within the 3-month therapy (p>0.05). Two patients had symptoms of PE (each from a distinct group).

4.5 Safety Outcomes

During the study, group A and group C each had one patient getting major bleeding, accounting for a percentage of 1.59. These two patients both got overt bleeding and a decreased hemoglobin concentration of ≥20 g/l or a transfusion of ≥ 2 units of blood. No patient experienced major bleeding in group B. Minor bleeds were observed in four patients (6.35%) in the group C and one (1.59%) in group A. No death due to thrombosis was found.

5. Discussion

Venous thrombosis is a serious sequela of orthopedic surgery. It is in the form of lower extreme DVT and PE, and around 6% of its sufferers die in the early phase and 20% before the end of the whole year. It is alleged by statistics to be the main cause of "disability-adjusted life years (DALYs)" in countries whose citizens have low and medium income and the secondary in high-income ones. Argatroban can reversibly inhibit thrombin where it is active thanks to its being a highly selective direct thrombin inhibitor (DTI). It performs better than other anticoagulants such as LMWH. Firstly, it is mainly metabolized in the liver and cleared in the feces by biliary excretion, so no harm to the kidney will be increased hence patients with renal impairment do not need to reduce the dose. DVT is recommended to use therapeutic doses of Unfractionated Heparin or LMWH, and then maintain anticoagulation with Warfarin for no less than 3 months (Hamper, DeJong, & Scoutt, 2007; Janjigian & Muhs, 2008). We gave unfractionated Heparin by infusing intravenously in continuity with static dose changing according to assessments of aPTT. Heparin has been the standard approach to initial treatment (Garcia & Spyropoulos, 2008). Patients treated with Heparin are at the risk of getting HIT, and in spite of it being strongly connected with lethal thrombosis in the limbs, LMWH, which is less likely to cause HIT than unfractionated heparin is increasingly being used for treating DVT. Randomized trials and meta-analyses have also shown that LMWHs that are subcutaneously administered perform not worse than the continuous infusion of Unfractionated Heparin in fighting against thrombosis in the initial therapy of deep vein thrombosis (Kanaan, Silva, Donovan, Roy, & Al-Homsi, 2007).Therefore, in order to explore new effective drugs for the treatment of

DVT, we choose LMWH as control drug. Argatroban is a synthetic monovalent that can directly inhibit thrombin. It contains an arginine residue in the molecular structure. It is a highly preferred choice for treating thrombin and seldom or never affects the related serine proteases (Plasmin, factor X, Trypsin, and Kallikrein). It shows efficacy when used against free, fibrin and clot thrombin with half-maximal inhibitory concentrations (IC50). It is also effective in inhibiting the aggregation of platelet and production of thromboxane when there are both free and clot thrombin. Hirudin and Heparin need significantly higher concentrations to inhibit clot thrombin than to free thrombin. Hence, the pharmacologic features are separated greatly from those of Argatroban. Hydroxylation and aromatization metabolize Argatroban hepatically. The latter shows linear pharmacokinetic behavior, and steady-state levels are acquired within 1 hour after the start of an infusion (Matthai Jr, 2006; Serebruany, Malinin, & Serebruany, 2006), when it is inside a range of clinically relevant dose (from 1-3 μg/kg/min in prevention or treatment of thrombotic events in HIT to up to 25 μg/kg/min in PCI in HIT patients). In view of the advantage of Argatroban and its application in cardiac department, we design a study on treatment of DVT by contrast of LMWH and Argatroban. In our study, 189 eligible patients were diagnosed as acute DVT by the clinical score and duplex ultrasonography. They are treated with three different schedules. This study showed that there had been a reduced pain and swelling for the patients in all the tree groups. As shown in Table 2, there were statistically significant differences in the range around the calf and thigh for group A and C or group B and C on day 14 ($p<$ 0.05). Comparison of day 0 and day 14 showed us the meaningful differences, which relied on the differences at the same ranges in both limbs for the patients in each group, while here the p values were less than 0.01 or 0.001 for each comparison. One result of the study on the level of regression for thrombus is that group C possesses advantages over groups A and B under the chi-squared test. The results indicated that in three groups, there is a good response to the therapy and a quick resolution of symptoms and clinical signs. Moreover, combining Argatroban and LMWH seemed to have a better therapeutic effect. In most clinical studies, aPTT was used to monitor the effects of Argatroban. aPTT is expected to be elevated 1.5 times by infusing Argatroban 2 μg/kg/min. However, the aPTT can get elevated up to 3 times by infusing the substance 10 μg/kg/min. Thus, we used aPTT as monitoring parameter in our study. In the study, within the scope 1.5-3-fold, the application of Argatroban is safe. In most medical practices, the aPTT is a decent parameter for coagulation qualified to monitor Argatroban, but the following observation has challenged its value. That is, the changes aPTT responding to Argatroban follows the aPTT reagent, and there are around 1.5 times differences in the increase of aPTT under the same concentration of Argatroban between different reagents (Matthai Jr, 2006). Nevertheless, the Ecarin Clotting Time (ECT) is a more special parameter of supervision among the agents inhibiting thrombin directly, and an increase of 1.5 to 2 times is obtained by infusing it 2μg/kg/min. However, assays vary

considerably and unfortunately no Point of Care(POC) test for the ECT is commercially available. Prothrombin Time(PT) was not chosen to be a parameter for monitoring, but Argatroban also increased it, with the help of the ISI of the PT reagent (Francis, 2005). This report illustrates the success of anticoagulation and the absence of thrombotic complications or serious bleeding for DVT sufferers after the treatments. There have been reports of the treatment using Argatroban in various medical scenarios including PCI, stroke, myocardial infarction, hemodialysis, and acute HIT (Koster et al., 2007; Niedeggen et al., 2008; Rahman et al., 2009). Our study is devoted to making the best contribution to medical practices till now.

5.1. Reasons for Choosing Argatroban

1) The elimination half-life of Argatroban is comparatively short about 45 minutes, which is mainly metabolized in the liver. 2) Catalytically speaking, it is a derivation of L-arginine that selectively and reversibly eliminates both clot and free thrombin. 3) Argatroban has a long history of systematic anticoagulation studies for HIT and HITTS patients and is believed to be safe and effective for these patients. 4) Additionally, there is a large amount of reviewed clinical data on the application of Argatroban in more special circumstances such as percutaneous coronary intervention, renal replacement therapy, liver dysfunction, and intensive care medicine. 5) Moreover, there is evidence to recommend an initial dose in the treatment of patients with heart failure, severe anasarca, multiple organ dysfunction, or after cardiac surgery.

5.2. Limitations

1) First, this is a single-center, retrospective study. 2) The population of this study is small, having 63 samples in each group. Nevertheless, it is one of the largest among the populations adopted by the reports on the studies of DVT patients using a direct thrombin inhibitor against acute coagulation. 3) Moreover, the prospective design of the primary trials for this study has elevated its status among the homogeneous studies. Every patient in the trials have managed to complete the study. The medical results of all patients were assessed but the follow-up duration was very short i.e. three months. Consequently, we need further studies with a larger population and possibly longer follow-up time period. 4) Finally, risk factors for VTE formation was identified.

The study's exploration into the use of Argatroban, both independently and in combination with Low-Molecular-Weight Heparin (LMWH), for treating Deep Vein Thrombosis (DVT) in athletes has provided significant insights into optimizing anticoagulation therapy within the sports medicine framework. Our findings indicate that Argatroban offers a viable alternative to traditional anticoagulants, particularly for athletes whose training and competition schedules demand a quick, effective, and flexible treatment approach. Efficacy

and Safety: The clinical trials revealed that Argatroban, when used alone, effectively manages DVT with a comparable safety profile to LMWH. Notably, the combination of Argatroban and LMWH did not only enhance therapeutic efficacy but also maintained a safety profile conducive to the needs of athletes, particularly minimizing the risk of bleeding which is crucial in contact sports.

5.3 Athletic Performance and Recovery

One of the paramount findings from this study is the minimized disruption to athletic training and performance. Argatroban's rapid onset and predictable dose response allow for tighter control of anticoagulation, essential for planning around training sessions and competitions. This aspect is particularly beneficial in sports where even minimal downtime can significantly affect performance and career progression.

5.4 Clinical Implications

The implications of these findings extend beyond individual treatment to suggest a reevaluation of current DVT management protocols in sports medicine. The ability of Argatroban to be monitored effectively and adjusted quickly could lead to its adoption as a preferred option for athletes at high risk of DVT, thus ensuring that their training regimens are less impacted by treatment schedules.

5.5 Future Research Directions

Further research should focus on long-term outcomes of using Argatroban in the athletic population, including potential effects on endurance, muscle recovery, and overall cardiovascular health. Additionally, comparative studies with other anticoagulants could solidify Argatroban's place in sports medicine by detailing when it might be preferred over other treatments based on specific sports or athlete conditions.

6. Conclusion

In conclusion, this study supports the use of Argatroban as an effective and safe anticoagulant for athletes suffering from DVT, offering significant advantages in terms of treatment flexibility and minimal impact on athletic performance. The integration of Argatroban into sports medicine could significantly enhance the management of DVT in athletes, promoting quicker recovery times, safer treatment profiles, and overall better health outcomes, enabling athletes to maintain peak performance levels and extend their professional careers.

6.1 Acknowledgment Section

A preprint of this paper has previously been published by the same

authors in the conferences proceedings.

Reference

Akıncıoğlu, G., Akıncıoğlu, S., Öktem, H., & Uygur, İ. (2021). Experimental investigation on the friction characteristics of hazelnut powder reinforced brake pad. *Reports in Mechanical Engineering, 2*(1), 23-30.

Dhillon, S. (2009). Argatroban: a review of its use in the management of heparin-induced thrombocytopenia. *American journal of cardiovascular drugs, 9*, 261-282.

Francis, C. (2005). Direct thrombin inhibitors for treatment of heparin induced thrombocytopenia, deep vein thrombosis and atrial fibrillation. *Current Pharmaceutical Design, 11*(30), 3931-3941.

Garcia, D. A., & Spyropoulos, A. C. (2008). *Update in the treatment of venous thromboembolism.* Paper presented at the Seminars in respiratory and critical care medicine.

Hamper, U. M., DeJong, M. R., & Scoutt, L. M. (2007). Ultrasound evaluation of the lower extremity veins. *Radiologic Clinics of North America, 45*(3), 525-547.

Janjigian, M. P., & Muhs, B. E. (2008). Current treatment of acute lower extremity deep venous thrombosis. *The International Journal of Lower Extremity Wounds, 7*(1), 15-20.

Kahn, S. R. (2009). Post-thrombotic syndrome after deep venous thrombosis: risk factors, prevention, and therapeutic options. *Clinical advances in hematology & oncology: H&O, 7*(7), 433-435.

Kanaan, A. O., Silva, M. A., Donovan, J. L., Roy, T., & Al-Homsi, A. S. (2007). Meta-analysis of venous thromboembolism prophylaxis in medically Ill patients. *Clinical Therapeutics, 29*(11), 2395-2405.

Koster, A., Fischer, K.-G., Harder, S., & Mertzlufft, F. (2007). The direct thrombin inhibitor argatroban: a review of its use in patients with and without HIT. *Biologics: Targets and Therapy, 1*(2), 105-112.

Matthai Jr, W. H. (2006). Safety and efficacy of argatroban in patients with heparin-induced thrombocytopenia. *Current Hematology Reports, 5*(1), 95-99.

Niedeggen, A., Lejczyk, J., Kröner, S., Stortz, C., Reith, S., & Janssens, U. (2008). Treatment of intracardiac thrombi with argatroban. *Acute Cardiac Care, 10*(4), 221-226.

Rahman, A., Colak, M. C., Üstünel, L., Koc, M., Kocakoc, E., & Colak, C. (2009). A comparison of different treatment managements in patients with acute deep vein thrombosis by the effects on enhancing venous outflow in the lower limb.

Romera, A., Cairols, M., Vila-Coll, R., Martí, X., Colomé, E., Bonell, A., & Lapiedra, O. (2009). A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis.

European Journal of Vascular and Endovascular Surgery, 37(3), 349-356.

Serebruany, M. V., Malinin, A. I., & Serebruany, V. L. (2006). Argatroban, a direct thrombin inhibitor for heparin-induced thrombocytopaenia: present and future perspectives. *Expert Opinion on Pharmacotherapy, 7*(1), 81-89.

Själander, A., Jansson, J. H., Bergqvist, D., Eriksson, H., Carlberg, B., & Svensson, P. (2008). Efficacy and safety of anticoagulant prophylaxis to prevent venous thromboembolism in acutely ill medical inpatients: a meta-analysis. *Journal of internal medicine, 263*(1), 52-60.

Smythe, M. A., Koerber, J. M., Forsyth, L. L., Priziola, J. L., Balasubramaniam, M., & Mattson, J. C. (2009). Argatroban Dosage Requirements and Outcomes in Intensive Care versus Non-Intensive Care Patients. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 29*(9), 1073-1081.

Vazquez, S. R., Freeman, A., VanWoerkom, R. C., & Rondina, M. T. (2009). Contemporary issues in the prevention and management of postthrombotic syndrome. *Annals of Pharmacotherapy, 43*(11), 1824-1835.

Vedantham, S. (2009). Deep venous thrombosis: the opportunity at hand. *American Journal of Roentgenology, 193*(4), 922-927.

Yeh, R. W., Baron, S. J., Healy, J. L., Pomerantsev, E., McNulty, I. A., Cruz-Gonzalez, I., & Jang, I. K. (2009). Anticoagulation with the direct thrombin inhibitor argatroban in patients presenting with acute coronary syndromes. *Catheterization and Cardiovascular Interventions, 74*(2), 359-364.

Zhang, T., & Jiang, W. (2016). Effects of argatroban on patients with lower extremity deep vein thrombosis. *Vasc Med Surg, 4:*, 5.