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DOCTORAL THESIS

**THROMBOEMBOLIC COMPLICATIONS
IN ORTHOPEDIC PATHOLOGY**

A B S T R A C T

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TABLE OF CONTENTS

List of published works	VII
List of abbreviations	IX
Index of Figures	XI
Index of tables	XIII
Thanks	XV
INTRODUCTION	XVI

THE GENERAL PART

1. Traumatic and orthopedic pathology	1
1.1. Sprains	1
1.1.1. General	1
1.1.2. Incidence of sprains	2
1.1.3. Complications of sprains	3
1.2. Dislocations	4
1.2.1. General	3
1.1.4. Sprain treatment	4
1.2.2. Incidence of dislocations	4
1.2.3. Complications of dislocations	5
1.2.4. Treatment of dislocations	6
1.3. Fractures	7
1.3.1. General	7
1.3.2. Incidence of fractures	8
1.3.3. Complications of fractures	8
1.3.4. Fracture treatment	10
1.4. Osteoarthritis	12
1.4.1 General	12
1.4.2. Incidence of osteoarthritis	12
1.4.3. Treatment of osteoarthritis	13
2. Deep venous thrombosis	15
2.1 Definition	15
2.2. Incidence	15
2.3. Symptomatology	15
2.4. Diagnosis	16
2.5. Risk factors	18
2.6. Pathophysiology	20
2.7. Prophylaxis	22
2.8. Treatment	23
2.9. Complications	24
3. Pulmonary thromboembolism	25
3.1. Definition	25

3.2. Incidence	26
3.3. Symptomatology	26
3.4. Diagnosis	26
3.5. Risk factors	28
3.6. Pathophysiology	29
3.7. The obstructive mechanism	29
3.8. The vasoconstrictor mechanism	30
3.9. Prophylaxis	31
THE SPECIAL PART	
Study 1: Incidence of deep vein thrombosis in patients with lower limb fractures	33
1.1. Materials and methods - Study 1	36
1.2. Results - Study 1	37
1.3. Discussions - Study 1	39
1.4. Risk scores	44
1.5. Stage conclusions - Study 1	47
Study 2: Conservative treatment of fractures increases the risk of deep vein thrombosis compared to surgical treatment in animal models	48
2.1. Materials and methods - Study 2	51
2.2. Results - Study 2	55
2.3. Discussions - Study 2	58
2.4. Stage conclusions - Study 2	62
Study 3: Lymphocytes and neutrophil/lymphocyte ratio are not predictors of mortality in patients with hip fractures	64
3.1. The experimental part - Study 3	65
3.2. Results and discussions - Study 3	66
3.3. Stage conclusions - Study 3	71
Study 4: Postoperative thrombophlebitis, major risk of pulmonary thromboembolism	74
4.1. Materials and methods - Study 4	76
4.2. Outcome - Study 4	77
4.3. Discussions - Study 4	80
4.4. Results - Study 4	87
4.5. Conclusions - Study 4	88
FINAL CONCLUSIONS	90
REFERENCES	92

Keywords: orthopedic pathology, complications, thromboembolism, experimental models.

INTRODUCTION

Orthopedic pathology is a complex one and includes a wide range of acute conditions (local trauma - fracture, sprain, dislocation). These acute conditions can lead to serious systemic consequences, namely deep vein thrombosis, pulmonary embolism, joint instability, gonarthrosis. In view of these aspects, it is necessary to observe all the rules of prophylaxis that the orthopedic doctor has. Starting from this premise, I chose the topic of this doctoral thesis and together with my mentors to set the purpose of this study. One of the most important problems, in the case of ankle and foot injuries, is deep vein thrombosis, always being a challenge for diagnosis and treatment. The predisposing factors, in the case of sprains, are the vascular lesions that can convert the antithrombogenic endothelium into a thrombogenic one and the prolonged immobilization that favors stasis. It is known in the literature that the DVT rate in patients with proximal femoral fracture is 5 times higher than in cases of lower knee fractures, while in the case of femoral shaft fractures or distal femoral fractures, the rate is about 3 to 4 times larger. However, the occurrence of DVT in patients with lower knee fractures is documented, independent of the administration of prophylactic antithrombotic medication. Manafi Rasi A. et al. highlighted that DVT is not a common complication of immobilization located below the knee, chemoprophylaxis should not be considered in the presence of less than 3 risk factors. Deep vein thrombosis defines a pathology that results from the formation of a blood clot (thrombus) in a deep vein in the lower limb. Deep vein thrombosis tends to occur in the veins of the lower limbs, such as the popliteal or femoral veins, as well as deep veins in the pelvis. DVT management is usually conservative with systemic anticoagulants to prevent the spread of existing thrombi, the formation of new DVT, and pulmonary embolism (PE). Deep vein thrombosis causes significant mortality and morbidity, these cases becoming a financial burden for the community. This is one of the main reasons why I chose this topic.

THE SPECIAL PART

Study 1: Incidence of deep vein thrombosis in patients with lower limb fractures.

The aim of this study was to calculate the incidence of deep vein thrombosis among hospitalized patients.

Thus, a study was performed at the Orthopedics and Traumatology Clinic in Cluj-Napoca, verifying information from the period 0.01.2017-31.12.2017. Our inclusion criteria were inpatients who received surgical treatment for fractured lower limbs as well as Doppler ultrasound. The exclusion criteria were closely related to chronic treatment with oral anticoagulants and reoperation operations. Our inclusion criteria were: inpatients who received surgical treatment for fractured lower limbs as well as Doppler ultrasound and comorbidities; diabetes, obesity, smoking, alcohol consumption, myocardial infarction, congestive heart failure, kidney failure, stroke or cancer. Ultrasounds were performed by the same doctor in all cases. Patients were positioned on their backs, and the iliac and femoral veins were scanned bilaterally. Deep vein thrombosis was diagnosed where complete vein compression was not possible and the thrombus was visible in mode B. Examinations were performed using the MyLab® Gold 25 system.

All patients received low molecular weight heparin thromboprophylactic treatment (enoxaparin or nadroparin) at a dose of 0.4 ml if the patient weighed less than 60 kg and 0.6 ml if the patient weighed more than 60 kg. Pharmacological prophylaxis was initiated 12 hours after trauma and was discontinued 12 hours before surgery.

The information gathered included age, sex, comorbidities, type of fracture, type of operation, its duration and the result of Doppler ultrasound.

Statistical analysis was performed using GraphPad Prism 6.0. We calculated the means, standard deviations, correlation test and unequal variation test. The distribution was calculated using the Saphiro-Wilk test. The results were considered statistically important if the p value was less than 0.05. According to the inclusion and exclusion criteria, we found 175 patients with fractured lower limbs who received a Doppler ultrasound. The average age was 74.4 years (21-96). There was an acetabular fracture, 139 fractures of the proximal extremity of the femur, 10 fractures

of the femoral shaft, 3 fractures of the distal femur, 18 fractures of the leg and 4 fractures of the ankle.

The average time from presentation to surgery was 5 days (between 0 and 18 days). The types of operations performed were: There were: 1 acetabular fracture, 139 fractures of the proximal extremity of the femur, 10 fractures of the femoral shaft, 3 fractures of the distal femur, 19 fractures of the leg and 4 fractures of the ankle. Comorbidities were present in 128 patients, and the most common were: high blood pressure (46.8% cases), cardiovascular disease (39.4%) and diabetes (14.2%). Deep vein thrombosis was present in 52 cases (29.7%) and was located as follows: common femoral vein (35 cases), deep femoral vein (6 cases), superficial femoral vein (10 cases), iliac vein (2 cases), popliteal artery (5 cases) and posterior tibial vein (1 case).

Seven cases had two areas of deep vein thrombosis. No patient had clinical manifestations of pulmonary embolism during hospitalization.

There were no statistically significant differences between patients with deep vein thrombosis and those without, in terms of age ($p = 0.4$) and comorbidities ($p = 0.1$). We found important differences in the days of hospitalization before surgery ($p < 0.0001$) (an average of 3.6 days for patients without DVT and 8.4 days for patients with DVT). No links were observed between age and hospitalization days before surgery ($r = -0.03$). A moderately positive correlation was observed between deep vein thrombosis and the presence of cardiovascular comorbidities ($r = 0.51$), and a weakly positive correlation was observed between DVT and hypertension, respectively diabetes mellitus ($r = 0.26$ and $r = 0.3$). Our study did not show correlations between DVT and age, stroke, hypercholesterolemia or other comorbidities.

Femoral fractures increased the risk of DVT by approximately 5 times compared to below-knee fractures in hospitalized patients.

Study 2: Surgical treatment versus conservative treatment of animal fractures

For this study, 30 male Wistar albino rats, 10 weeks old, weighing 200 ± 30 grams were used.

The animals were kept at a standard temperature of 21.5°C and a light / dark cycle of 12 hours. Foods in the form of granules and water were offered ad libitum.

Prior to randomization, a veterinarian declared the subjects clinically healthy. This study was approved by the Ethics Commission and the National Sanitary Veterinary and Food Safety Authority (no. 120 / 06.06.2018). The experiments were performed in accordance with current national and international legislation at the Center for Experimental Medicine Cluj-Napoca, Romania. The great diversity of genetically modified mouse strains allowed a better understanding of the blood clotting cascade and the fibrinolytic system. Numerous genes encoding proteins associated with platelet, endothelial, or vascular smooth muscle cells have been targeted in mice. The study was approved by the Ethics Commission and the National Sanitary Veterinary and Food Safety Authority (no. 120 / 06.06.2018). The experiments were performed in accordance with current national and international legislation at the Center for Experimental Medicine Cluj-Napoca, Romania. Prior to randomization, a veterinarian declared the subjects clinically healthy. Subjects were divided into three groups, as follows: Group I (bilateral deep vein thrombosis), Group II (bilateral deep vein thrombosis, unilateral tibial fracture, intramedullary stem fracture fixation), and Group III (bilateral deep vein thrombosis, fracture unilateral tibia, conservative fracture treatment).

Deep vein thrombosis model

The procedure was performed bilaterally for all groups. In Group II rats (n = 10), the fracture was fixed with an anterograde intramedullary rod. Thus, with a knee flexion of 90 degrees, an incision was made centered on the patellar tendon of the rat.

After longitudinal dissection of the patellar tendon fibers, the tibial plateau was spotted. The spinal canal was opened with a 19G needle. A 20x1mm intramedullary titanium rod (Ti90Al6V4) was subsequently inserted to stabilize the fracture. In the end, the subcutaneous tissue was closed with resorbable threads, and non-absorbable threads were used for the skin. Tetracycline ointment was applied to the site of surgery.

Conservative treatment technique

Following the fracture and thrombosis of the ipsilateral femoral vein in Group III, the leg was immobilized in a splint. The technique of applying the splint consisted in the use of two wooden rods (middle and side) and a bandage on the entire

circumference of the foot. Menthol gel was applied daily to the surface of the bandage to prevent rats from damaging it. If the integrity of the splint was compromised, it was applied again. For 10 days after the start of treatment, rats were monitored daily to determine their general condition. Histological examination After 10 days of surgical procedures the rats were euthanized using general anesthesia and cervical dislocation. The legs and lungs were harvested and placed in 10% formaldehyde.

Hematoxylin and eosin staining were used in both femoral vein and lung investigations. The femoral veins were examined bilaterally to find DVT, the degree of obstruction (total or partial) and the length of the obstruction. The lungs were cut and the presence of venous emboli was checked. Fatty pulmonary embolism was also examined using safranin staining in the intramedullary stem group.

Sample size and strength were measured before grouping with StatMate software. Statistical analysis was calculated using GraphPad Prism 6.0 and included means, frequencies, standard deviations, correlation tests, and the t-student test for equal variations. The results were considered statistically important if the p values were less than 0.05. During the study, a Group III subject died from an anesthetic overdose. None of the subjects had respiratory problems or impaired general condition during the experiment. Histological examinations of the pulmonary system showed a higher incidence of complete obstruction of the pulmonary arteries in Group I, 50% (n = 5/10) compared to Group II, 10% (n = 1/10) and Group III, 9% (n = 1/9). The mean degree of artery obstruction in Group I was $86\% \pm 19.55$, higher compared to Group II ($57\% \pm 29.83$, $p = 0.04$) and Group III ($70\% \pm 24.5$, $p = 0.36$). No significant differences were found between Groups II and III ($p = 0.5$). To our knowledge, this is the first study in the literature to evaluate the effects of different fracture treatments on deep vein thrombosis in animals. The lack of clinically relevant respiratory symptoms and deaths in rats (except for anesthetic overdose) leads to the conclusion that there were no major cases of pulmonary embolism.

STUDY 3: Lymphocytes and the neutrophil / lymphocyte ratio as predictors of mortality in patients with hip fractures

At this stage, a retrospective observational study was performed in a single center, with data collected prospectively for survival. The main objective of this study was to determine whether inpatient hemoglobin, lymphocyte count, and neutrophil

ratio to lymphocytes can be predictable for one-year survival of patients with hip fracture.

Patients with hip fractures, over 55 years old, hospitalized for surgical treatment were followed for a period of 9 months (Oct. 2015-Jun. 2016). Subsequently, the patient records were independently reviewed by 2 authors. 197 patients were included in the study, excluding those who were treated by total arthroplasty, spinal cord fixation or did not have surgical treatment. Age, sex, hemoglobin, neutrophils and interacting lymphocytes, as well as the type of surgery were recorded in Excel (Microsoft Office 10). The haematological picture was determined using ADVIA 2120 flow cytometry and spectrophotometry. Patients were then prospectively monitored until Oct. 2017 (1.25-2 years) when the survival rate of patients was assessed. The study was approved by the hospital's Ethics Commission and the Research Department. In order to evaluate the association between the studied parameters and the risk of death, logistic regression models were developed in which death was considered the result, and different parameters of the study were considered possible predictors. The study included 54 patients with femoral neck fractures, 119 with trochanteric fractures and 24 with subtrochanteric fractures. Displaced femoral neck fractures were treated by hemiarthroplasty, using partial endoprotheses (Biomet, Warsaw, USA). The influence of lymphocytes and the ratio of neutrophils to lymphocytes (N / L) were determined both in each of the 3 groups and as a whole. For femoral neck fractures, trochanteric and subtrochanteric fractures, the associations in the logistic regression model proved not to be significant, with p values of 0.837, 0.181 and 0.162 for lymphocyte and 0.920, 0.794 and 0.168 for N / L, respectively. When age, sex and hemoglobin were taken into account, pain for trochanteric fractures, age was an independent predictive factor with $p < 0.001$. In the current study, the absolute number of lymphocytes as well as N / L were not predictable for survival at 2 years after surgical treatment of a proximal femoral fracture. The lack of statistical significance was also found in the case of parameters such as hemoglobin at hospitalization and male sex, and the age parameter proved to be statistically significant only for the subgroup of trochanteric fractures.

STUDY 4: Effectiveness of prevention measures used in deep vein thrombosis.

The aim of the study was to identify the effectiveness of preventive measures used in deep vein thrombosis in two hospital units. The study included the Department of Orthopedics and Traumatology within the Deva County Hospital, as well as the Timișoara County Emergency Clinical Hospital. The study was conducted over 5 years.

In the Department of Orthopedics and Traumatology at Deva County Hospital, between 2009 and 2014, there were 110 patients with unilateral or bilateral gonarthrosis in which conservative treatment was not effective, which is why we opted for total knee arthroplasty. Of the 110 patients at Deva County Hospital, 35 (18%) were diagnosed with chronic venous disease in the affected lower limb and were referred for surgical resolution. Total knee arthroplasty was performed 8-12 weeks after surgical resolution of chronic venous disease, using a standard operating protocol. Prophylactic measures were applied to all patients and included: administration of low molecular weight heparin in prophylactic doses, starting with 2 hours preoperatively and administration for 2 weeks postoperatively; maintaining hydroelectrolytic balance to prevent increased blood viscosity, early postoperative mobilization (passive mobilization on the first postoperative day associated with isometric contractions; active mobilization on the 4th postoperative day), compressive bandage until joint recovery, administration of oral anticoagulants or Tr Symptom - starting with day 11 postoperatively and continuing for 6 weeks with periodic check-up - Quick time between 30-40% and INR between 1.8-2.5). As a result, the 35 patients with a mean age of 58.7 years were mostly cases of women (66.67%). A number of 12 patients (40%) presented comorbidities: chronic ischemic heart disease - 6 (20%), grade II / III obesity - 4 (13.3%) and atrial fibrillation - 2 (6.66%). Considering the clinical examination, the 35 cases were classified according to the staging of chronic venous insufficiency (CEAP) as follows: Stage I (5 cases): varicose veins - in 4 cases they were present only in the affected lower limb, and in 1 bilateral case; Stage II (18 cases): varicose veins - in 8 cases they were present only in the affected lower limb, and in 3 cases they were present bilaterally; Stage III (5 cases): varicose veins, perimaleolar edema, muscle cramps, paresthesias, restless legs syndrome; Stage IV (4 cases): varicose veins, stasis dermatitis, perimaleolar edema, dermohypodermatitis; Stage V (3 cases): varicose

veins, scarred ulceration. No patients operated for the treatment of chronic venous insufficiency had postoperative complications. Regarding total knee arthroplasty, there were 4 cases of postoperative thromboembolic complications (12.9%). 2 cases of deep vein thrombosis (6.67%) that occurred in the postoperative days 7 and 10. Patients were placed in stage IV CEAP and were treated surgically for venous pathology before total knee arthroplasty. They also showed signs of popliteal-femoral thrombosis with edema in the lower limb. The treatment was conventional and included: 5000 units heparin, intravenously every 4 hours for 7 days, associated in the last 3 days with oral anticoagulants (Sintrom or Thrombostop), under the control of Quick time (25-30%). Subsequently, the treatment with Sintrom was continued for 3 months postoperatively, bed rest with the affected lower limb in a prone position, anti-inflammatory and analgesic treatment; 1 case of symptomatic pulmonary embolism (3.3%), which occurred 8 days after surgery, in a patient in stage V CEAP, also treated surgically for venous pathology before total knee arthroplasty. The patient also showed atrial fibrillation and followed the treatment initiated by the cardiologist. Clinical examination and electrocardiographic examination indicated symptomatic pulmonary embolism with dyspnea, atrial fibrillation, chest pain, and cough with bloody sputum. Specific treatment included: 5000 IU heparin, intravenously every 4 hours for the first 10 days + Oral thrombostop from day 7 for 6 months + papaverine 500 mg intravenously + oxygen therapy + intravenous myophillin + slow intravenous digoxin. The evolution was favorable, and the symptoms were remitted, without further complications. The patient with chronic venous insufficiency class 2 CEAP who refused the surgical treatment of venous pathology, before the surgery of total knee arthroplasty developed on day 7 postoperatively deep venous thrombosis at the ilio-femoral level, resistant to the specific treatment described above. The patient also developed chronic edema in the leg and thigh, which persisted despite 6 months of treatment with dicoumarins. Prevention of deep vein thrombosis with reduced doses of low molecular weight heparin significantly reduced the incidence of deep vein thrombosis. Calcium or sodium heparin 5000 units is administered subcutaneously two hours before surgery and thereafter every 8-12 hours.

CONCLUSIONS

1. Deep vein thrombosis remains a common complication of limb fractures, with an increased risk of morbidity and mortality especially due to pulmonary embolism.
2. Routine administration of anticoagulants decreases the risk of deep vein thrombosis, but there is still a rate of patients who develop deep vein thrombosis regardless of the associated treatment.
3. Distal femoral fractures, surgical procedure using gamma rods, and a history of stroke are frequently associated with higher rates of deep vein thrombosis.
4. Conservative treatment has a higher risk of deep vein thrombosis compared to surgical treatment.
5. Active limb mobilization in cases of deep vein thrombosis leads to a higher rate of pulmonary embolism.
6. Moreover, fatty pulmonary embolism in the group treated with intramedullary rods is often encountered without endangering life, according to our study.
7. The result of Study 3 did not show any notable or clinically useful predictions regarding the survival of patients with hip fractures by using perioperative lymphocyte count and neutrophil count to lymphocytes.
8. Study 4 highlights the benefits of using fractional heparin, which is easy to administer in combination with elastic restraint. In conclusion, these 2 treatments improved the postoperative results of elective surgery in abdominal and vascular surgery in patients with moderate or increased thromboembolic risk.
9. It is imperative to carry out larger and larger-scale prospective studies that are able to confirm this prevalence of DVT.
10. This may result in a re-evaluation of current VTE prophylaxis guidelines as the main beneficiary of the results being this group of patients.