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Medicine

CONSERVATIVE TREATMENT OF FRACTURES INCREASES THE RISK OF DEEP VEIN COMPARED TO SURGICAL TREATMENT IN ANIMAL MODEL

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ABSTRACT: *FRACTURES ARE A COMMON FINDING IN TRAUMA DEPARTMENTS WORLDWIDE AND THEY CAN BE TREATED CONSERVATIVELY OR SURGICALLY. IN BOTH TYPES OF FRACTURE TREATMENT, DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE) ARE LIFE-THREATENING COMPLICATIONS. AN ANIMAL MODEL WAS USED TO STUDY THE INFLUENCE OF TREATMENT TYPE ON DVT AND PE INCIDENCE. THIRTY RATS WERE EQUALLY DIVIDED INTO THREE GROUPS AS FOLLOWING: GROUP I (BILATERAL FEMORAL VEIN THROMBOSIS), GROUP II (BILATERAL VEIN THROMBOSIS AND UNILATERAL TIBIA FRACTURE TREATED SURGICALLY) AND GROUP III (BILATERAL VEIN THROMBOSIS AND UNILATERAL TIBIA FRACTURE TREATED CONSERVATIVELY). THE TOTAL OBSTRUCTION OF THE FEMORAL VEIN IPSILATERAL TO THE FRACTURE WAS FOUND IN 60% OF CASES IN GROUP I, 50% OF CASE IN GROUP II AND 100% OF CASES IN GROUP III. REGARDING THE FEMORAL VEIN THROMBOSIS IN THE NON-FRACTURED LIMB, THE TOTAL OBSTRUCTION OF THE FEMORAL VEIN WAS OBSERVED IN 50% FOR GROUP I, 60% FOR GROUP II AND 11% FOR GROUP III. COMPLETE OBSTRUCTION OF THE PULMONARY ARTERIES WAS 50% IN GROUP I, 10% IN GROUP II AND 9% IN GROUP III. FAT PULMONARY EMBOLISM OCCURRED IN 6 OUT OF 10 CASES IN GROUP II. CONSERVATIVE TREATMENT HAS A HIGHER RISK OF DEEP VEIN THROMBOSIS COMPARED TO SURGICAL TREATMENT. FURTHERMORE, PULMONARY FAT EMBOLISM IN THE INTRAMEDULLARY NAIL TREATED GROUP IS FOUND IN MOST CASES, WITHOUT CLINICAL SYMPTOMS.*

KEY WORDS: FRACTURE, DEEP VEIN THROMBOSIS (DVT), PULMONARY EMBOLISM (PE), CONSERVATIVE TREATMENT, SURGICAL TREATMENT.

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INTRODUCTION

Fractures represent a common pathology worldwide affecting all ages, while the main clinical manifestations include pain and functional impairment. Treatment of fractures can be either conservatively or surgically, and despite the good overall result, complications can occur. Deep vein thrombosis (DVT) is a common complication and can lead to pulmonary embolism which is the most common cause of death in patients with lower limb fractures treated both surgically or conservatively.

Deep vein thrombosis occurs when the elements of the Virchow's triad (venous stasis, hypercoagulability and/or endothelial lesions) are present. DVT rate varies with the anatomic site of the injury reaching up to 80% for patients with femur fractures. The risk factors associated with DVT in trauma patients are represented by polytrauma patients, pelvic, femoral or tibia fractures, spinal cord lesions, elderly population and other medical comorbidities (e.g. obesity, diabetes, renal failure, malignancies, congenital or acquired coagulation disorders).

Due to the high incidence of DVT in patients with fractures of the lower extremity where immobilization is recommended, anticoagulation prophylaxis is usually indicated. The 9th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines indicates thromboprophylaxis after major orthopaedic surgery such as knee/hip fractures, but it is does not recommend the use of thromboprophylaxis in patients with isolated lesions located distal to the knee.

The thromboprophylaxis methods can be divided in: pharmacologic prophylaxis, mechanical methods and inferior vena cava filters. Pharmacologic prophylaxis with anticoagulation includes administration of low-dose heparin (LDH), low molecular weight heparin (LMWH), and factor Xa inhibitors. Mechanical methods of prophylaxis include graduated compression stockings (GCSs), pneumatic compression devices (PCDs), and A-V foot pumps. Pharmacologic prophylaxis with LMWH and the use of pneumatic compression devices, showed a significantly decrease of venous thromboembolism in trauma patients.

Currently, there is no prospective research to study the influence of surgical versus conservative treatment in terms of DVT and PE incidences. The only data currently available resulted following retrospective studies. The complex interactions between fractures, DVT and PE can only be studied in vivo. The purpose of the study was to identify which of the treatments (conservative or surgical) has the highest risk of DVT and PE.

MATERIALS AND METHODS

Animal model

The study was approved by the Ethics Commission, as well as Sanitary Veterinary and Food Safety Agency (no. 120/06.06.2018). The experiments were conducted according to current national and international legislation and were conducted at the Centre of Experimental Medicine Cluj-Napoca, Romania. A total of 30 male albino Wistar rats, 10 weeks old, with a weight of 200±30 grams, took part in the experiment. The animals were kept at a standard temperature of 21.5°C and 12 hours' dark/light cycle. Pellet food and water was provided ad libitum. Prior to randomization, the subjects were declared clinically healthy by a veterinary doctor. The subjects were equally divided into three groups as follows: Group I (bilateral deep vein thrombosis); Group II (bilateral deep vein thrombosis + unilateral tibia fracture + intramedullary nail fixation of fracture); Group III (bilateral deep vein thrombosis + unilateral tibia fracture + conservative treatment of fracture).

Fracture model

The procedure was performed unilaterally (left limb) in groups II and III. The rats underwent general anaesthesia using a cocktail of Ketamine (0.08ml / 100g) and Xylazine (0.04ml / 100g). After induction of anaesthesia, the hair was removed from the operative field, and the skin was prepared with Betadine. An anterior incision of approximately 1 cm length in the middle of the calf was performed. The tibial bone was exposed, and it was fractured with a chisel in the middle third of the diaphysis. Subcutaneous cellular tissue was sutured with resorbable wires and the skin was closed with nonresorbable wires followed by Tetracycline application on the postoperative wound.

Deep vein thrombosis model

The procedure was performed bilaterally and in all of the groups. An incision of approximately 1.5 cm length from the inguinal ligament to the distal medial thigh was performed. After dissection of the anatomical planes, the neurovascular bundle was identified and carefully dissected under the microscope to isolate the deep femoral vein over a 1 cm (Figure 1a, Figure 1b). A direct application on the femoral vein of a 10% ferric chloride solution for 2 minutes was done, according to a previously described technique. Finally, obstruction of the femoral vein proximal to the site of thrombosis was tested by venous refill from the proximal end (Figure 1c). Subcutaneous cellular tissue was sutured with resorbable wires and the skin was closed with nonresorbable wires followed by Tetracycline application on the postoperative wound.

a b c

Figure 1. Deep vein thrombosis model. Visualization of neurovascular bundle (a). Separation of femoral vein (b). Femoral vein thrombosis following application of 10% ferric chloride solution (c).

Intramedullary nail implantation - surgical treatment

In the case of rats from Group II (n = 10) fracture fixation was done with an anterograde intramedullary nail. Thus, with a knee flexion of 90 degrees, was performed an incision centered on the rat's patellar tendon. After the longitudinal dissection of the patellar tendon fibers, the tibial plate was spotted. The tibial medullary canal was opened with a 19G needle. Subsequently, a titanium intramedullary nail (Ti90Al6V4) of 20x1mm was introduced to stabilize the fracture. At the end, the subcutaneous tissue was closed with resorbable wires and skin with nonresorbable wires. On the operative site was put ointment with Tetracycline.

Conservative treatment technique

Following the fracture and thrombosis of the ipsilateral femoral vein in Group III, the leg was immobilized in a splint. The splinting technique consisted in application of two wooden nails (medially and laterally) and a band-aid on the entire circumference of the leg (Figure 2). The firmness of the construct was checked daily. On the surface of the Band-Aid a mentholated gel was applied daily to prevent its degradation by the rats. If the integrity of the splint was damaged, the splint was reapplied.

Figure 2. Splinting of fracture leg in conservative treatment group.

Ten days following the initiation of treatment, the rats were monitored daily for deterioration of general status.

Histological analysis

Ten days following the surgical procedures, the rats were euthanized by general anaesthesia and cervical dislocation. The bilateral legs and lungs were harvested and placed in 10% formaldehyde after preparation.

Haematoxylin-eosin staining was used in both femoral vein and lung investigations. Bilateral femoral veins were examined for presence of deep vein thrombosis, degree of obstruction (total or partial) and length of obstruction. The lungs were sliced and checked for venous emboli. Fat pulmonary embolism was also examined using safranin orange staining in case of intramedullary nail group.

Statistics analysis

The sample size and power were calculated prior to group allocation using StatMate® software and a significance level of 0.05 two-tailed was used. The statistical analysis was calculated using GraphPad Prism 6.0 software and included means, frequencies, standard deviations, correlations tests and student T-test for equal variances. The results were considered statistically significant if p-values were < 0.05.

RESULTS

During the study, one subject in Group III died due to an anaesthetic overdose. None of the subjects showed clinical respiratory problems or impairment of the general status throughout the experiment.

Deep vein thrombosis

Histological examinations showing complete obstruction (Figure 3a) and partial obstruction of femoral vein (Figure 3b). Both types of obstruction were found in all groups.

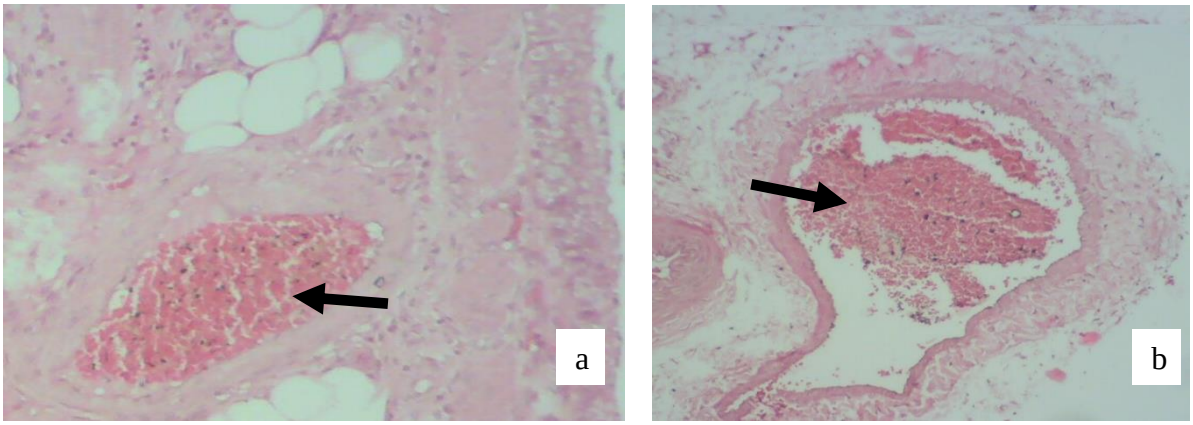

Figure 3. Histologic examinations of femoral vein thrombosis.

Histological examinations of the left limb (fractured limb in treatment groups) showed that total obstruction of the femoral vein ipsilateral to the fracture was found in 60% of cases in Group I, 50% of case in Group II and 100% of cases in Group III. The average length of thrombosis was 13.7 mm for Group I, 15 mm for Group II and 15.3 mm for Group III.

Regarding the femoral vein thrombosis of the right limb (non-fractured limb in the treatment groups), the total obstruction was present in 50% for Group I, 60% for Group II and 11% for Group III. The average length of the obstruction was 13 mm for Group I, 13 mm for Group II and 15.2 mm for Group III.

Conservative treatment group had a statistically significant lower incidence of total obstruction for the contralateral limb ($p=0.02$ vs. Group I and $p=0.02$ vs. Group II).

The total length of total and partial obstructions for bilateral femoral veins was: 25.3 mm for Group I, 28 mm for Group II and 30.5 mm for Group III. The total length of thrombosis in case of Group III was statistically significant higher compared to Group I ($p=0.048$).

In both treatment groups, the non-fractured limb had a lower incidence of complete obstruction compared to fractured limb, but the only statistically significant difference was observed in Groups III ($p<0.05$).

Pulmonary embolism

Histological examination on the pulmonary system showed a higher incidence of complete obstruction of the pulmonary arteries in the Group I, 50% (n=5/10) comparative to the Group II, 10% (n=1/10) and Group III, 9% (n=1/9) (Figure 4). The average degree of artery obstruction in the Group I was 86%±19.55, higher compared to Group II (57%±29.83, $p=0.04$) with statistical significance and to Group III (70%±24.5, $p=0.36$). Moreover, there were not found significant differences between Groups II and III ($p=0.5$).

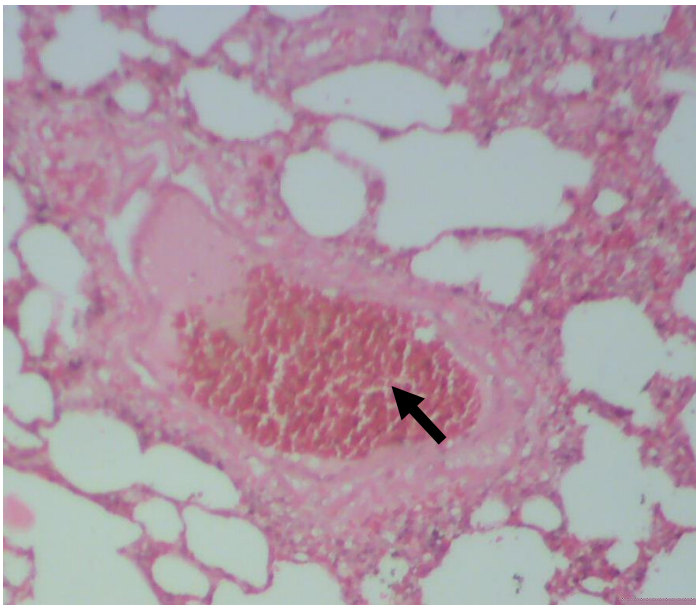

Figure 4. Histological examinations showing complete obstruction.

Regarding the fat pulmonary embolism evaluated in the Group II, these occurs in 6/10 cases (Figure 5).

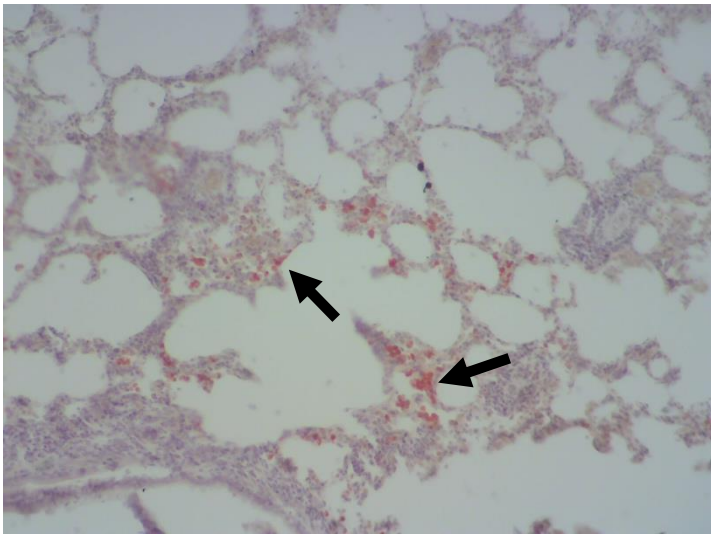

Figure 5. Safranin orange stain in group II showing fat pulmonary embolism.

DISCUSSIONS

To our knowledge, this is the first study in the literature to evaluate the different fracture treatments' effect on deep vein thrombosis in animal model.

The absence of clinically relevant respiratory symptoms and deaths in rats (except the one found in the case of anaesthetic overdose) means that no major pulmonary embolism has occurred. The highest incidence of a complete obstruction of the ipsilateral femoral vein in case of conservative treatment compared to intramedullary nail is more likely due to the impaired muscle pump found in case of conservative treatment. The early mobilization made possible

when surgical treatment is used lowers the risk of deep vein thrombosis. Although the incidence of complete obstruction of the ipsilateral leg in case of surgical treated fractures and control group are the similar, the length of the obstructions was higher in case of surgically treated group. This shows the thrombogenic effect of the fracture, of the surgery, or most likely, both. The conservative treatment group had the highest length of obstruction, which can be explained by the immobilization found in this group.

An unexpected result was regarding the incidence of complete obstruction in case of contralateral limb. The lowest incidence was found in conservative treatment group. This result can be explained by the fact that the subjects in Group III had used the contralateral limb to a greater extent compared to the other groups. This leads to a better muscle pump actions and a better prevention of thrombogenic effects in the contralateral limb.

Concerning the pulmonary embolism rate in rats with DVT bilaterally, there were differences in the control group compared to the other groups, significant for the intramedullary nails treated group. It is known that the rate of embolism is higher in subjects with non-immobilized DVT compared to immobilized subjects, which confirms the results of the current study. The higher degree of mobility in subjects with DVT alone facilitates the migration of the thrombus into the lungs with increased risk of pulmonary embolism. On the other hand, the degree of pulmonary embolism was lower in the fracture group of the tibia diaphysis treated with intramedullary rods compared to the immobilized group. This highlights that total immobilization of fractures-adjacent joints in a subject with DVT is a PE risk factor compared to subjects with intramedullary fixation that allows movement of adjacent joints and weight-bearing as tolerated.

Fat pulmonary embolism was evaluated only in the intramedullary nail treated group because in this situation there is a higher risk of mobilization of fatty emboli. The results of our study showed that in one third of the surgically treated cases the fat embolism rate was high while in another third the fat embolism was minimal. In these cases, there were only a few limited areas of fat embolisms identified by optical microscopy in the coloration of Safranin orange. In the other cases (n=4) no fat emboli was found. The incidence of pulmonary fat embolism in patients with long bone fractures is low (2-5%) but can occur in trauma patients. Early surgical fixation of the fracture followed by immobilization of the limb significantly reduces the risk of this complication.

Limitations of the study includes a relatively low number of subjects. Therefore, some differences could not be proved to be statistically significant, as well as lack of pulmonary fat embolism determination in groups I and III.

CONCLUSION

Conservative treatment has a higher risk of deep vein thrombosis compared to surgical treatment. Active limb mobilization in cases with deep vein thrombosis leads to a higher pulmonary embolism rate. Furthermore, pulmonary fat embolism in the intramedullary nail treated group is often encountered without necessary being life-threatening, according to our study.

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