NEWS IN PREVENTING VENOUS THROMBOEMBOLISM IN ELDERLY PATIENTS WITH PROXIMAL FEMORAL FRACTURE

FILIP PANAIT[1]

[1]*PhD candidate "Lucian Blaga" University of Sibiu*

Keywords: *thromboembolism, prevention, anticoagulants*

Abstract: *The prevention of Venous Thromboembolism (VTE) in case of elderly patients with proximal femoral fracture benefits from a more and more complex range of anticoagulants which reduce the risk of pulmonary thromboembolism, a severe complication involving life-threatening risks.*

Cuvinte cheie: *tromboembolism, profilaxie, anticoagulante*

Rezumat: *Profilaxia tromboembolismului venos (TEV) în cazul bolnavilor vârstnici cu fractură de femur proximal beneficiază de un arsenal din ce în ce mai complex de anticoagulante care reduc riscul producerii tromboemboliei pulmonare, complicaţie severă cu risc letal ridicat.*

Venous Thromboembolism (VTE) represents the occurrence of a blood clot (thrombus) inside the blood vessels, due to an unbalance between the coagulant factors, in excess, and the anticoagulant factors, less than necessary. VTE is enabled by the presence of the Virchow's triad–endothelial injury, venous stasis, hypercoagulability.(1,2)

Initially, Venous Thromboembolism appears in the form of Deep Vein Thrombosis (DVT), and in secondary stage as Pulmonary Thromboembolism (PTE). But prospective cohort studies reported cases in which PTE manifested as an incipient form of VTE, with a mortality rate of 7-11%.(3)

In the USA, it is estimated that symptomatic thromboembolism is affecting 600000 of patients every year, of which 100000 die of pulmonary thromboembolism.(3,4,5) In case of young patients, the occurrence of thromboembolism is much decreased, while in elderly patients as much as 1000 cases of 100000 may occur every year.(6) In case of patients with orthopedic surgeries, the incidence may be of 40-65%, without prevention, the maximum risk of occurrence of VTE being present in the first 2 weeks, after which, for 2-3 months, the risk is still great. PTE occurs at approximately 3-7 days after a DVT burst and can be lethal within an hour after occurrence, in 10% of the cases.(3,7,8)

Prevention of thromboembolic diseases

In the guidelines of ACCP IX (American College of Chest Physicians ed. IX 2012), venous thromboembolism is studied from the perspective of some multidisciplinary groups in order to obtain an efficient and comprehensive response.

In medical practice, there are used three methods of preventing the thromboembolic diseases: general methods, mechanical methods and pharmacological methods.

The general methods of preventing the thromboembolic diseases consist in the decrease of hemoconcentration, by appropriate hydration, early mobilization of the patients presenting a thromboembolic risk and those who can walk, active or passive mobilization of the inferior limbs in immobilized patients.(7)

The mechanic prevention of thromboembolic diseases is achieved by elastic compression with bandages or elastic stockings, by intermittent pneumatic compression devices, leg vein pumps, electrical stimulation of shank muscles, Trendelenburg position, and active limb movements, based on indications, especially in patients with a high risk for major bleeding complications, or as an adjuvant in pharmacological prevention of thromboembolic diseases.(2,4)

The pharmacological prevention of thromboembolic diseases uses several classes of anticoagulant substances: antiplatelet drugs (antiaggregants), oral anticoagulants, fibrinolytic and heparin drugs.

Antiplatelet drugs (antiagreggants): aspirin (irreversible inhibitor of cyclooxygenase), indobufen and flurbiprofen (reversible inhibitors of cyclooxygenase), dipyridamole (inhibates phosphodiesterase), clopidogrel and ticlopidine (inhibit the binding of ADP to the platelet surface).

Vitamin K antagonists (VKA)

Before the discovery of heparins, the main anticoagulants were the vitamin K antagonists (VKA). The most popular VKA is warfarin. More recently, there have been introduced other products on the market, such as: acenocumarol and fluindione, with an increased specificity, an anticoagulant action limited only to one factor in the coagulation chain.

In order to use them it is necessary to analyze the INR (International Normalized Ratio), defined as a comparative rating of a patient's prothrombin time and the standard prothrombin time, corrected with the ISI index, by means of a complex formula accepted by the World Health Organisation (WHO).(7,9)

For femoral fractures surgeries, a normal INR is considered to have values between 2,0 and 3,0. In patients with mechanic valve prosthesis, a normal INR has values between 3,0 and 4,0. A low-dose increases the risk of thromboembolism, expressed by a low INR, an overdose, proved by an increased INR, raises the risk of bleeding. After VKA therapies, cases have been reported of cutaneous necrosis in patients with protein

[1]Corresponding author: Filip Panait, Str. Gutuiului, Nr. 52, Comuna Bâra, Judeţul Neamţ, România, E-mail: panait.filip@yahoo.com, Tel: +40233 765516

Article received on 20.11.2012 and accepted for publication on 07.01.2013
ACTA MEDICA TRANSILVANICA March 2013;2(1):214-217

deficiency, due to the reduced synthesis of all vitamin-K dependent proteins.(7,9)

The disadvantage of using them is represented by the fact that they ensure a narrow therapeutic panel, having a slow response (48-96 hours) after administrating the treatment and after that the effect is slowly decreasing, extending the anticoagulant effect and the risk of bleeding, especially in case of emergency surgery.(9)

Unfractionated heparins (UFH) are acid lineal polysaccharides of the glycosaminoglycan family with an anticoagulant effect, inactivating thrombin and the activated factor X (Xa) by antithrombin III (ATIII). Unfractionated heparins are extracted from the mucosal tissues of porcine intestine or bovine lung and have an average molecular weight ranging from 10 to 20kDa.(7,10,11)

Unfractionated heparins (UFH) are used for the prevention of VET, in a dose of 5000 UI, subcutaneously, every 8-12 hours. The use of UFH is not recommended in the patients with hemorrhagiparous syndromes, such as hemophilia and thrombocytopenia, presenting high risks of bleeding: active ulcer, upper gastrointestinal hemorrhages, lower gastrointestinal hemorrhages, genital hemorrhages or other recent hemorrhages.(4,7)

It is necessary to act with care when administering UFH in patients with uncontrolled hypertension, severe liver failure and major traumatisms. The side effects after the administration of UFH are thrombocytopenia, especially after an extended treatment, therefore it is necessary to monitor the platelet level, before and after the treatment. Unfractionated heparins are preferred in severe kidney failure (creatinine clearance <30 mm/min), due to the fact that they are not eliminated by the kidneys, compared to the low molecular weight heparins (LMWH), eliminated by the kidneys.(3)

The UFH treatment requires individualized doses for each patient and imposes frequent measures of Activated Partial Thromboplastin Time (APTT).

Low Molecular Weight Heparins (LMWH) are more frequently used in hip fractures, due to the possibility of rapidly controlling their effects, the low risk of bleeding;they do not require precise monitoring of anticoagulation level through APTT and the thrombocytopenic effect is reduced. The lower incidence of hemorrhages is linked to the minimum antiplatelet effect and the absence of an increased vascular permeability. The prevention of thromboembolic diseases can be initiated pre-operatory or post-operatory, with comparable results. In case of low molecular weight heparins (LMWH) treatment, it is necessary to monitor the kidney function, especially in the patients with kidney failure.

The ACCP IX guidelines are not very specific on the dosage of antiplatelets, recommending the use of the dosage set by the manufacturer.(4)

It is recommended to use some antiplatelets which do not affect the kidney function or the use of small doses, the monitoring of the kidney function and the blood level of the anticoagulant.

Emergency surgery, in patients treated with antiplatelets containing clopidogrel or aspirin, which require a 5-day period for the reconstruction of the platelet mass, must be performed carefully, in order to be able to promptly intervene in case of bleeding complications.(7) In these situations, the perioperative interruption of treatment with antiplatelet agents does not work, due to the irreversible inhibition of the platelet activity, mediated through ADP receivers - for clopidogrel and by cyclooxigenase - for aspirin.

In the patients who do not need emergency surgery, it is necessary to interrupt the antiplatelet treatment, 5 days before the surgery and to continue with a "bridge" treatment, with short-time antiplatelets, such as eptifibatides, tyrophiban or with unfractionated heparins, administered intravenously or with LMWH (Fraxiparin), administered subcutaneously, in a small dose.(9)

Types of LMWH:

Fondaparinux, trade name Arixtra, marketed as solution for injection of sodium Fondanparinux in doses of: 1,5mg/0,3ml, 2,5mg/0,5ml, 5mg/0,4ml, 7,5mg/0,6ml, 10mg/0,8ml. Fondaparinux is a low molecular weight heparin, obtained synthetically, functioning as anti-factor Xa. For prevention, doses of 2,5 mg/day are administered, subcutaneously, 6-24 hours post-operatorily, not being allowed to use it pre-operatorily, due to the risk of bleeding.(7,12) In case of femoral neck fractures, the use of Fondaparinux is elective, having results proven by studies accredited at trust level 1A.

The treatment recommended by the producer must be continued 5-9 days, until the patient gets mobilized; only in special situations it can be extended by another 24 hours.

Fondaparinux is used cautiously in the patients with mild or moderate kidney failure, with creatinine clearance of 30-80 ml/min, in the patients with active gastrointestinal ulcerations. In elderly patients, the risk of bleeding is increasing due to the drop of the kidney clearance and the accumulation of Fondaparinux, which requires caution.

In severe kidney failure, with creatinine clearance bellow 20 ml/min, it is not recommended to use Fondaparinux.(3) Fondaparinux therapy must be initiated and continued, considering the fact that there is no known antidote for it.

Dalteparina, most known in Romania according to its trade name, Fragmin.

It is traded as: Fragmin 2500 UI/ml sodium Dalteparina anti-factor Xa, to 1 ml for injection, Fragmin 2500 ml/0,2 ml, Fragmin 5000 UI/ml, Fragmin 7500 UI/0,3ml, Fragmin 10000 UI/ml, Fragmin 15000 UI/0,6 ml.

An algorithm describing the steps for the optimal drug administration can be the following: 5000 UI Dalteparina subcutaneously, the night before the orthopedic surgery, after which, it is continued with other 5000 UI after the intervention, for at least four hours after the surgery. Also, the treatment can be administered on the day of the surgery, with no more than two hours before it, in a dose of 2500UI Dalteparina, subcutaneously, followed by another dose of 2500 UI Dalteparina, subcutaneously, 8-12 hours after the surgery, not sooner than 4 hours after the intervention, in order to prevent the post-operatory bleeding. Until the completion of the treatment, 5000 UI Dalteparina, subcutaneously, every morning should be administered.

In certain situations, Dalteparina can be administered post-operatorily, 2500 UI, subcutaneously at 4-8 hours, the minimum 4-hour interval must be maintained for this treatment scheme as well, after which it is continued every day with 5000 UI Dalteparina, subcutaneously, until the completion of treatment. Dalteparina treatment can be extended up to five weeks after the surgery and can be continued in ambulatory care, using the same algorithm as during hospitalisation.

Along with Dalteparina, the treatment with oral antithrombotic drugs such as VKA can be continued until obtaining a therapeutic prothrombotic activity. Dalteparina is recommended in mild or moderate kidney failure and can be administered in equal doses as for people who are not suffering from kidney failure.

In severe kidney failure, with a creatinine clearance below 30 ml/min, caution is recommended, as well as the

adjustment of the doses based on the plasma concentration of Dalteparina.(12) The normal plasma concentration of Dalteparina is of 0,5 to 1,5 UI/ml, measured at 4-6 hours after administration, the average being of 1UI/ml. After determining the plasma concentration, the dose should be adjusted, plus or minus, with 2500 UI at every administration, after which the concentration on a third or fourth administration should be measured again. The treatment with dalteparina is continued using the dosage obtained after adjustment.

Adverse reactions are generally valid for all LMWHs, hemorrhage, elevated value of liver transaminases, transitory thrombocytopenia, cutaneous necrosis.

The antidote for Dalteparina is Protamine Sulfate, 25-50% efficiency, 1 mg Protamine Sulfate inhibits the effect of 100 UI Sodium Dalteparina.

Nadroparina, in Romania having the trade name of Fraxiparine, is a conditioned injection, packed in prefilled syringes of 0,3ml, 0,4ml, 0,6ml, 0,8ml and 1ml of calcic-type nadroparina, which can be used as an antithrombotic with immediate, but also long term effect. Syringes of more than 0,6 ml are marked to allow the dose adjustment, when required by the value of the INR.

In orthopedic surgery, the manufacturing company is recommending the Fraxiparine treatment subcutaneously, one a day, adjusted according to the patient's body weight.(7) The administration must be completed based on the following pre-operatory algorithm, 12 hours before the intervention:

- Under 50 kg: 0,2 ml;
- From 50 to 69 kg: 0,3 ml;
- Over 70 kg: 0,4 ml.

The treatment must be continued post-operatory, 12 hours after the intervention, until the 3rd day, after the 4th day, the following treatment scheme will be used and will be continued for a minimum of 10 days:

- Under 50kg: 0,3 ml;
- From 50 to 69kg: 0,4 ml;
- Over 70 kg: 0,6 ml.

The warnings regarding the administration of Fraxiparine are those valid for all LWMHs. In case of an overdose, hemorrhages can appear which can be minor and are treated by reducing the dose or by totally interrupting the administration. In this case, the half-life period being reduced, the anticoagulant effect drops rapidly. Exceptionally, an antidote can be used as Protamine Sulfate, which inhibits the anticoagulant effect of Fraxiparine: 0,6 ml of Protamine Sulfate neutralizes 0,1 ml of Fraxiparine.

In the patients with thromboembolic diseases caused by preexisting diseases, it is necessary to continue the treatment with oral anticoagulant drugs which are administered at first, with Fraxiparine until the normalization of INR. In these situations, Fraxiparine treatment becomes a "bridge" treatment between the pre-operatory and post-operatory period, necessary for the accurate control of the anticoagulation effect throughout the surgical intervention.

Enoxaparina is a LMWH also used for mild or medium kidney failure, without adjusting the dose and in severe kidney failure, it is cautiously used, reducing the dose to half or increasing the time period between the doses, from 12 to 24 hours.(12)

In Romania, the most known product is Clexane, which contains 100 mg enoxaparin/1ml and it is marketed in prefilled syringes, of 20mg/0,2ml, 40mg/0,4ml, 60mg/0,6ml, 80mg/0,8ml or 100 mg/1ml.

In the patients with a moderate thrombotic risk, it is administered in 20 mg/0,2 ml, sc, at 24 hours.

In the patients with a great thrombotic risk it is administered in 40 mg/0,4 ml/day, sc starting 12 hours pre-operatorily, with a prefilled; after that the treatment, it is repeated daily, until the patient's complete mobilization.

Enoxaparine is administered subcutaneously in the abdominal plication.

Caution is recommended when associating oral anticoagulants, AINS and corticosteroids. Care is recommended in treating patients with liver failure, patients with a history of gastroduodenal ulcer, severe high blood pressure, drugs uncontrolled.

In the patients receiving anticoagulant therapy based on salicylates (aspirin) or Clopidogrel, it is necessary to evaluate the hemorrhage risk and, eventually, to interrupt the treatment, 5 to 7 days before the surgery.

In the patients receiving a dual treatment, aspirin and Clopidogrel, it is recommended to undertake the necessary measures to prevent the post-operatory hemorrhages.

Adverse reactions when administering Enoxaparina: thrombocytopenia, hematoma caused by the syringe needle, hemorrhagiparous syndromes or modifications of transaminases and of alkaline phosphotase.(9) In all these situations the administration of Enoxaparina should be interrupted. Contraindications of Enoxaparina: thrombocytopenia in previous treatments with heparins, infective endocartitis, hypersensitivity (allergies) to Enoxaparine.

Length of thromboembolic diseases prophylaxis

The ACCP IX guidelines recommend pharmacological prevention of thromboembolic disease for 5-10 days in the hospital and draws the attention on the risk of Vein Thrombosis for a 60-day period post-operatorily, in major orthopedic interventions (femoral neck fractures, total hip prosthesis).(4)

Conclusions:

The Venous Thromboembolism (VTE) represents an important public health issue with a major impact on the people's health and influences the economic life of the contemporary society, by its relatively increased mortality.

The use of some treatments with greater specificity, such as Low Molecular Weight Heparins (LMWH), administered subcutaneously, represents a huge step in preventing Venous Thromboembolism and Lung Thromboembolism, as a severe form of the most frequent complications.

REFERENCES

1. Haines ST. Improving the quality of care for patients at risk for venous thromboembolism. American Journal of Health-System Pharmacy. 2010;67(10Suppl 6):S3-S8.
2. Ghelase MŞ, Borugă A, Râmboiu S, et al. Studiul factorilor de risc şi prevenţia tromboembolismului venos în chirurgie, Craiova medicală. 2008;10;1:16-21.
3. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism. The task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Heart Journal. 2008;29:2276-2315.
4. Clagett GP, Anderson AJr, Heit J, Levine MN, Wheeler BH. Prevention of Venous Thromboembolism, Chest, Journal of the American College of Chest Physician. 2012;ISSN 0012-3692Suppl:321S-334S.
5. Haines ST. Improving anticoagulant use for prevention of venous thromboembolism. American Journal of Health-System Pharmacy. 2010;67(10Suppl 6), S1-S2.
6. Vesa Ş, Crişan S, Macarie A, Donca V, Ghidrai O. Prevalenţa factorilor de risc pentru tromboza venoasă

profundă a membrelor inferioare- diferenţe legate de vârstă. Clujul medical. 2012; LXXXIII, 2:295-301
7. Gherasim L, Antonescu D, Tulbure D. Ghid de prevenţie a tromboembolismului venos. Ordinul Ministerului Sănătăţii nr.1391/2010. MO partea I nr. 95.2011.
8. Roca IC, Aursulesei V, Roca M, Cimpoeşu D, Datcu MD. Studiu comparativ asupra impactului factorilor de risc chirurgical la pacienţii cu tromboembolism venos, model de analiză al riscului de deces, Iaşi, Jurnalul de Chirurgie. 2012;8,1:23-29.
9. Rugină M, Sălăgean M, Predescu L, Apetrei E. Noi anticoagulante orale. Romanian Journal of Cardiology. 2012;22:1:43-52.
10. Zhang Z, McCallum SA, Xie J, Nieto L, Corzana F, et al. Solution structures of chemoenzymatically synthesized heparin and its precursors. Journal of the American Chemical Society. 2008;130:39:12998-13007.
11. Zhang F, Yang B, Ly M, Solakyildirim K, et al. Structural characterization of heparins from different commercial sources. Analytical bioanaytical chemistry. Springer. 2011;401,9:2793-2803.
12. Dager WE. Issues in assessing and reducing the risk for venous thromboembolism. American Journal of Health-System Pharmacy. 2010;67(10Suppl 6),S9-S16.