UNIVERSITY OF MEDICINE AND
PHARMACY CRAIOVA

PARTICULAR ASPECTS
OF ANTI-THROMBOTIC
TREATMENT IN HIP
ARTHROPLASTY

ABSTRACT

Ph.D student
DR. TRUȘCĂ PAUL TIBERIU

SCIENTIFIC COORDONATOR
PROF. DR. VALENTIN CÂRLIG

CRAIOVA, 2010
During the progress of orthopedic surgery, one of the most important elements was the
essential contribution of orthopedics at improving quality of life in elderly patients suffering
of osteoarthritis, through arthroplasty. Historically, the hip joint was the first one which was
replaced in order to treat osteoarthritis, and these types of operations became more and more
frequent. Due to increased life expectancy, society faced the problem of finding the technical
and economical means to give these patients a normal life, not affected by their arthritis. So,
the number of the implanted hip prosthesis grew up continuously, and, reflecting this thing,
the medical community became more and more interested in evaluating the safety and
efficacy of the method, including the complications of this type of surgery.

The results showed that the most important general complication of hip arthroplasty is
VENOUS THROMBO-EMBOLISM (VTE), producing the THROMBO-EMBOLIC
DISEASE, with two types of syndromes: acute (Deep Venous Thrombosis and Pulmonary
Embolism) and chronic (Post-Thrombotic Syndrome and Pulmonary Hypertension). Venous
thrombosis involves existence of a blood clot formed in the absence of bleeding, within a
vein, and which is obstructing blood flow.

The difference between coagulation and thrombosis is that, while coagulation is the
physiological response of the human body in order to stop bleeding, resulting the clot,
 thrombosis is a pathological process developing mostly without previous bleeding, resulting
the thrombus. The blood clot is a solid mass that is formed by blood coagulation. It contains
platelets, red blood cells and a protein called fibrin. Normally, the clots are part of the
haemostasis mechanism, which aims at preventing and stopping bleeding. When, through the
action of various factors, a blood vessel ruptures, some blood elements, such as platelets and coagulation factors, are activated.

The importance of these complications is reflected first of all by their incidence without treatment, which is 40-60% for DVT, 4.00 % for PE and 1.65 % for Fatal PE. More than that, the number of deaths in Europe (2007) due to thromboembolism was higher than the sum of those produced traffic accidents+ breast cancer+ prostatic cancer+AIDS. These data demonstrates that:

1. VTE has a significant impact on the morbidity and mortality of patients after hip arthroplasty, affecting the quality of the patients’ life and increasing the costs.

2. Hip arthroplasty is a” high risk procedure” from the point of view not only of the operation itself, but also concerning the risk of thrombo-embolic events, including the fatal ones

This is the reason of choosing the problem of preventing VTE after hip arthroplasty as the theme of this study, which is conducted in one of the hospitals with considerable experience both in hip arthroplasty, but also in assessing and treating the thrombo-embolic complications after surgery.

**Chapter I - “Theoretical Study”** reflects the general level of knowledge in this field. It starts with the basic aspects, such as: the anatomy of the hip, the types of prostheses and the venous system of the inferior limbs, not from the point of a thorough description of the surgical technique, but in order to prepare the sub-chapters directly connected to the theme of the study.

So, the pathology of thrombosis is analyzed starting with the Virchow triad: stasis, increased viscosity and tisular pro-thrombotic factors. In terms of epidemiology, factors belonging to Virchow's triad are found in the case of total hip arthroplasty, and they can be systematized as follows:

1. Factors contributing to venous stasis:
   - Lack of changing the positions of various segments of the body during and post-operatively
   - Decreased muscle contractility by hypotrophy post-immobilization
   - Obstacles in venous and lymphatic drainage - position during surgery, scars and fibrous blocks postoperatively
• Valvular system damage

2. Factors that cause blood viscosity growth
   • Dehydration, intra-operatively or postoperatively
   • Intra-operatively acute bleeding, with the "consecutive circulation"
   • Capillary permeability increase, consecutive to intra-operative hypoxia
   • Rebalancing deficiencies

3. Pro-thrombotic tissue factors produced during surgery are released from triturated muscle during surgery and due to hemorrhage

   All these are to be considered specific thrombotic risk for hip arthroplasties and their close connection to surgery explains the incidence of VTE. According to the principles of evidence-based modern medicine, the epidemiology of VTE, as reflected in international multicenter studies, underlines two ideas, which are very important for prophylaxis and treatment:

   1. Hip arthroplasty has a significant thrombo-embolic risk, so specific prophylactic measures have to be identified and applied, and
   2. The risk of VTE after hip arthroplasty lasts for a long period after surgery, indicating that long-term prophylaxis is mandatory in order to decrease the risk of VTE and improve the quality of the life

   The explanation for this long-term risk is represented by the fact that all the circumstances activating the Virchow Triad are long-standing, so the modern attitude is that thrombo-prophylaxis needs to be continued for THE WHOLE PERIOD WHEN THE RISK FACTORS ARE ACTIVE.

   The risk factors have been thoroughly studied and nowadays there are clearly identified the circumstances which are more or less connected with thrombo-embolic complications. In order to evaluate their importance, they were divided into groups, each group being given a certain number of points, and the sum of these points is compared with the scale of global risk.

   The author tries to identify, most completely, thrombotic risk factors; they have resulted in different scales, where risk was measured in different ways. Whatever their differences, it has been concluded there are two types of thrombo-embolic risk factors:

   - Factors which belong to the patient, called predisposing factors, resulting from the patient’s pathology associated with the one for which the
orthopedic surgery is performed and its past, such as a history of thrombo-embolic, chronic heart failure, advanced age, varicose veins, obesity, immobilization, paralysis, mielo-proliferative diseases, pregnancy and post-partum, congenital or acquired thrombophilia, treatment with estrogen; their identification can be made by history and interdisciplinary clinical and paraclinical evaluation.

- exposing factors, characteristic to the disease, such as, acute medical illnesses, surgery, trauma, acute respiratory or cardiac failure, catheterization of central veins, in the case of orthopedic interventions in this category are included: factors characteristic for the disease for which the surgery is made but also factors characteristic for the procedure, which are present also at patients without other associated organic problems, and are due to the duration of the surgery that require special maneuvers and positions.

After establishing the groups at risk, the symptoms and the diagnostic methods for DVT are presented, in order to underline that a complete, thorough evaluation From the clinical point of view, the most important thing to remember is that there are frequent asymptomatic episodes of DVT and PE, but which may complicate with PE sometimes fatal.

Clinical diagnosis in DVT has several elements, some of them with a high specificity degree:

- Pain in the calf, getting more intense at foot dorsoflexia and at manual compression
- Swelling of the calf

If these symptoms occur, there will be a presumptive diagnosis of DVT and will proceed to:

- Doppler ultrasound with compression, if this is negative, thrombosis is excluded; if it is positive, the thrombi presence will need in most of the cases to be confirmed with venography, because it tells us clearly the place and the extent of thrombosis.

In the same part, “Theoretical study”, one sub-chapter is dedicated to prophylactic and curative treatment, which consists of three types of measures:

A. General measures, known as hygienic-dietary treatment, which combats, through non-specific measures, the factors included in Virchow's triad, namely:
- Early mobilization of the patient, favored by performing surgery to achieve firm fractures stabilization, and the use of elastic immobilization by using different devices, combats stasis
- Increased blood viscosity is combated by proper hydration of the patient
- Release of pro-thrombotic factors is prevented by adequate intake of oxygen, which stabilizes cell membranes and capillary permeability, preventing the action of lysosomal acid hydrolases, which, when released, lead to cell lyses with releases pro-thrombotic tissue and platelet factors.

B. Mechanical devices – this class has two type of components:
   a. Those improving the venous flow of the inferior legs; this effect can be produced by a variety of devices, such as elastic stockings, but it also includes the devices which produce intermittent compression stimulating the venous system.
   b. The inferior vena cava filters - began to be used in recent years and their effectiveness is greater when associated with other means of prevention.

C. Pharmacological treatment includes several groups of substances, addressing to the pathological processes leading to thrombus formation.

Thus,

- Platelet adherence and aggregation are antagonized by drugs that block the substances inducing these processes, but they have limited use after total hip arthroplasty, which is a high thrombo-embolic risk surgery.
- Thrombosis is initiated by an abnormal activation of the coagulation cascade, that is why the drugs currently used in prophylaxis and treatment of thrombosis are those effective in different steps of this cascade. Unfractioned Heparin (UFH) has more than a historic value, especially in the treatment of thrombosis, but Low Molecular Weight Heparins (LMWH) are the current standards in thrombo-prophylaxis -since they reduce most of the undesired effects of UFH- especially in major orthopedic surgery, which is unanimously recognized as a high thrombo-embolic risk one. Fondaparinux sodium, which indirectly affect Factor Xa, proved to have a high risk of bleeding and Vitamin K Antagonists (VKA) have a nonspecific mechanism of action, a slow onset and offset of anticoagulating activity, and a narrow therapeutic window, patients requiring frequent laboratory monitoring. New oral anti-coagulants
(more correctly they should be called anti-thrombotic, since their main therapeutically indication is to prevent thrombosis, at least this is what is has been studied until now) have been created in order to respond to the following major demands: we need more and more specific anti-thrombotic activity (so they inhibit only one factor of the coagulation cascade) and we need a predictable response after a fixed unique oral dose with less bleeding risk. The author presents these therapeutic groups and notes in each case, the advantages and disadvantages, and also the specific factors that must be taken into account in their use in thrombo-prophylaxis after total hip arthroplasty.

Chapter II – Objectives
The second part reflects the personal contribution of the author, who intends to:
- study the chosen cases,
- treat and monitory typical cases for the established theme, and
- establish an ALGORITHM applicable with personal characteristics to each of the patients, based on the individual thrombo-embolic risk, algorithm with two components:
  - the individual treatment (prophylactic and curative)
  - the individual protocol of monitoring the patient (clinical and paraclinical).

Chapter III - Material and method
The author study 120 patients operated between 1.01.2006 – 1.01. 2010 in the Orthopedics and Traumatology Clinic – Clinical Emergency Hospital Bucharest. The patients, with hip arthritis, sustained total hip arthroplasty. The criteria used for analyzing this group of patients were:

- the individual thrombo-embolic risk
- the prophylactic anti-thrombotic treatment- when to start, for how long, types of medicines,
- monitoring the patients- clinical examinations, Doppler compression ultrasound evaluations,
- the incidence of DVT- symptomatic and asymptomatic,
- the incidence of pulmonary embolism- symptomatic and asymptomatic,
Chapter IV - Results

The study group is analyzed both in terms of demographic characteristics, but also in terms of the anatomical and surgical characteristics, presenting the etiology of the arthritis, the type of prosthesis which was used for arthroplasty and associated pathology without entering into details of surgical technique; the aim of this type of analysis is to assess, in accordance with the theme of the paper, the features of these patients in terms of thrombo-embolism, and not in terms of the arthroplasty itself.

This fact once established, the author explores thrombo-embolic risk factors at these patients, who sustained total hip arthroplasty, which according to all risk scales and treatment guidelines accepted nowadays is considered as a "major thrombo-embolic risk factor".

In order to establish a therapeutic algorithm, the most important aspect of analysis was the type of anti-thrombotic treatment.

Before establishing the treatment, all the patients were assessed for thrombo-embolic risk following the CAPRINI SCALE OF RISK, which was kept for all the patients in order to connect the risk factors with further results. Due to the fact that all the patients had major surgery, someone might say that this scale is not important, since they are all included, per primam, in the “very high risk” category, but it was interesting to find out what risk factor could be detected besides surgery for these patients, some of them influencing not only THE DRUG used for prophylaxis, but also THE MOMENT when this was initiated (for example when the patient had previous chronic anti-coagulation with VKA for associated pathology, the VKA had to be replace pre-operative with Enoxaparine in a curative dose, which was continued in the same dose post-operative, too).

Considering the above-mentioned three types of prophylaxis:
- general methods of thrombo-prophylaxis were used for all the patients- hydration, early mobilization of the patient, and all the others
- Mechanical methods were used for all the patients as following: bilateral elastic stockings within surgery and adapted attitude after surgery (considering the patient’s tolerance)
- all the patients received pharmacological thrombo-prophylaxis, with: Enoxaparine (60 patients), Nadroparine (30 patients), Fondaparinux (4 patients) and Rivaroxaban (26
patients), and the patients were analyzed separated for these 4 groups, considering the outcome.

Due to the fact that the number of the patients who received Fondaparinux was too small, there are no significant conclusions to drop from these patients.

Considering the other two groups, the same criteria were used for analysis:
- demographic: age, sex;
- associated pathology- the patients were evaluated using the final number of points in the risk scale, in order to establish the severity of the associated thrombotic risk factors
  - type of prosthesis
  - etiology of arthritis
  - intra- and post-operative bleeding
  - the incidence of DVT and PE
  - the incidence of other complications.

It is to be mentioned that:
- the same protocol was followed in order to monitories all these patients and
- long-term prophylaxis was used for all, that is 35-42 days after surgery (according to international standards, excepting the patients who developed DVT or EP and needed curative treatment with UFH, according to protocols).

The results were:
- the mean age of the patients was: 66 yrs for the Enoxaparine group, 67 yrs for the Nadroparine group and 62 for the Rivaroxaban group;
- the total risk evaluation showed considerable higher risk in the patients treated with Enoxaparine than in the other two groups (as shown in Figure 1); mean values 14.5 for the Enoxaparine group, 8.5 for the Nadroparine group and 7.5 for the Rivaroxaban group
- the intra-operative bleeding was: 825 ml for the Enoxaparine group, 875 ml for the Nadroparine group and 785 ml for the Rivaroxaban group; considering the fact that the patients did not receive Rivaroxaban before surgery, the intra-operative bleeding for this group is not significant for the Rivaroxaban treatment, but to compare it with the bleedings from the other two groups where prophylaxis started before surgery (this is why the colour in Fig.2 is different, green from the Nadroparline and Enoxaparine, which are blue)

- the post-operative bleeding was: 785 ml for the Enoxaparine group, 700 ml for the Nadroparine group and 715 ml for the Rivaroxaban group; (Fig.2)

Fig.2- Intra and post-operative bleeding

As it is shown, there are no significant differences between the two groups, not even considering the above-mentioned impact of pre-operative thrombo-prophylaxis above intra-operative bleeding, demonstrating that for the three drugs presented the anti-thrombotic effect is clearly differentiated from the haemorrhagic one.

- the incidence of DVT was: 4/60 (6.66%) for the Enoxaparine group, 4/36 (11.1%) for the Nadroparine group and 1/26 (4%) for the Rivaroxaban group; (Fig.3)
Fig. 3- The incidence of DVT

Due to compare the results, we represent (even if the units are different) on the same chart the risk-evaluation and the incidence of DVT, as in Figure 4.

Figure 4- Risk scale and DVT

If we analyse the above results, we see that the best efficacy is in the Enoxaparine group, where, even the mean value of the risk score was almost double compared to the other two groups, the incidence of DVT was comparable or lower than the Nadroparine and Rivaroxaban groups.

- the incidence of other complications was almost similar considering: chronic oedema -4/66 (6.66%) for the Enoxaparine group, 2/36 (5.55%) for the Nadroparine group and 3/26 (11.4%) for the Rivaroxaban group; other adverse reactions (AR): 3.33% for the Enoxaparine group, 8.36% in the Nadroparine group and 7.88% for the Rivaroxaban group (Fig. 5)
Fig. 5- Chronic oedema and other adverse reactions

No patient in the studied group developed PE, but we refer only at asymptomatic PE, because only the patients who had clinical symptoms were evaluated using CT (due to standard protocols in our Hospital); this means that we have no information about asymptomatic PE, while we can be sure that there was no asymptomatic DVT in the studied group, since all the patients were monitored using Doppler compression ultrasound at the routine visits or whenever abnormal symptoms were detected.

The value of the compression Doppler ultrasound is clear; for the cases when the thrombus was visualized using ultrasounds, the venography confirmed the diagnosis. (Fig. 6, 7)

Fig. 6- Recent thrombosis of the external iliac vein
Chapter V - Discussions and Conclusions

Considering the importance of thrombo-prophylaxis after hip arthropalsty, the author discuss the following aspects:

- Validity of existing risk scales in the context of current pathology diversification,
- Methods of assessment of risk factors (history, clinical examination, complementary examinations)
- Ways to improve patient’s compliance to current treatment guidelines, which indicate the need for long-term prophylaxis
- Need for patients’ rhythmic monitoring (clinical and paraclinical).

Based on these discussions, the conclusions of the paper represent elements of immediate practical implication, in accordance with specific guidelines:

1. Considering the serious risk of thrombo-embolic total hip arthroplasty at patients undergoing this type of surgery, a long-term thrombo-prophylaxis (35 - 42 days) is required, in accordance with current therapeutic recommendations. This period may be prolonged for as long as the thrombo-embolic risk factors persist.

2. Non-pharmacological methods are debatable and optional, but thrombo-prophylaxis medication is mandatory.

3. The moment when pharmacological thrombo-prophylaxis is initiated depends on the associated risk factors and especially on the chosen drug, since some of the anti-thrombotics are indicated only post-operative.
Recent developments, of direct inhibitors of the coagulation factors, are still at the begining from the point of view of clinical experience, and have a better compliance (since they are orally administered) but limited indications.

4. If patient needs pre-operative thrombo-prophylaxis, **Low Molecular Weight Heparines** are to be chosen, especially those with a high anti Xa: anti IIa ratio. More than that, if patients needs curative pre-operative anti-thrombotic treatment, **Enoxaparine** is to be chosen.

5. Patients’ monitoring is essential not only considering the arthroplasty itself, but also the thrombo-embolic complications. Thus, patients should be instructed about the alarm symptoms and about the necessity of respecting the monitoring protocol established by the medical team.

6. A complete protocol of anti-thrombotic prophylaxis for a patient with total hip arthroplasty includes: correct assessment of the **risk score** (after the scale), complete **therapeutic and monitoring** protocol and optimal compliance of the patient.

7. Thrombo-embolic complications incidence in the study group fit the limits of those presented in the literature, proving treatment efficiency, as well as the symptomatic complications incidence.