THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

THE STUDY OF THE CAUSES OF THROMBOEMBOLIC COMPLICATIONS AND THE POTENTIAL METHODS OF PROPHYLAXIS IN PATIENTS UNDERGOING HIP AND KNEE REPLACEMENT SURGERY

by **GABRIELLA SZÜCS, M.D.**

Supervisor: **BÉLA FÜLESDI, M.D., FULL PROFESSOR**

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF CLINICAL MEDICINE

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INTRODUCTION

Without employing thromboembolic prophylaxis in patients undergoing total hip or knee replacement surgery, 40-70% of the patients develop deep vein thrombosis (DVT) in their distal veins and 10-20% in their proximal veins, while fatal pulmonary embolism (PE) occurs in 1-5% of the cases. The most effective method of preventing thrombosis and its complications is the prevention of DVT with appropriate prophylactic therapy. Thromboprophylaxis with standard heparin (unfractionated heparin – UFH) introduced in the 1970-ies, DVT associated morbidity and mortality significantly decreased, down to 20-35%. After introducing APTT dose adjusted UFH therapy these indicators further decreased, down to 12-16%. In addition to the medicinal prophylaxis, mechanical means (e.g. elastic banding on the lower limbs, compression stockings, intermitting pneumatic compression, plantar compression devices, knee moving devices) were also introduced.

The precise molecular structure of heparin and the relationship between its structure and biological effect were identified during the mid 1970-ies. The idea of fractionating heparin came during the end of that decade. The first low molecular weight heparin (LMWH) to be clinically effective and safe to use, namely Fraxiparine, was first produced in the Choay Institute of Paris at the end of the eighties. Within a fairly short period several similar LMWH products of different pharmaceutical companies obtained their respective marketing authorisations. The incidence of DVT significantly decreased with LMWH therapy maintained for an interval of 10-14 days, and after introducing prolonged LMWH prophylaxis in 1996, it further decreased, down below 10%. PE only occurred occasionally.

Nowadays, science is seeking for an answer on why do thromboembolic complications develop in almost 10% of the patients despite employing prophylactic therapy. Several studies were conducted on whether a genetic defect was the underlying cause of the complications in these patients; however, we are still unable to answer this question unequivocally. Thus, it is still unclear whether it is necessary to screen every patient undergoing joint replacement surgery for congenital thrombophilia and if it is confirmed what kind of prophylactic measures shall be taken to effectively prevent thromboembolic complications. It is also unclear that which diagnostic option provides sufficient information to recognize thromboembolic complications in time and prevent their complete development. Our workgroup seeks answers to these questions as well. In my current thesis I wish to provide information about the results of our completed work so far and present our current practice regarding thromboembolic prophylaxis.

OBJECTIVES

1. Our first task was to asses our results obtained with the then-available UFH therapy in patients, who underwent joint replacement surgery between 1984 and 1992, in order to establish a reference for the evaluation of the efficiency of the currently used newer methods.

2. During animal tests, we modelled the implantation of hip endoprosthesis thus studying the efficacy and safety of thromboembolic prophylaxis using an LMWH product. We searched for appropriate laboratory tests, which can serve as early indicators of thrombotic complications. We studied the level of Factor Xa inhibition, several haemostasis parameters, platelet count, and changes in fibrinogen levels during the perioperative period, which are important factors of thrombosis development.

3. Our objective was to improve our previous results obtained with UFH prophylaxis, with the help of new methods, which became available on the international scene. We evaluated our results obtained during the 10-day long LMWH prophylaxis and then the ones obtained during the prolonged LMWH prophylaxis scheme.

4. Another objective was to determine the panel of safe, reliable and low risk diagnostic methods, which can diagnose not only the completely developed thromboses but imminent thromboses as well, in order to start their therapy as soon as possible, thus preventing the complete development of this severe complication.

5. Recently, an increasing amount of observations support that thromboembolic complications occurring despite modern complex prophylaxis (physical and prolonged LMWH) are mainly due to some sort of genetic abnormality. Therefore, another objective was to assess the prevalence of thrombophilia in our patients, who underwent surgery and study the role of thrombophilia in those cases when complications occurred. We studied the correlation between the patients' risk score and the incidence of thromboembolic complications.

6. On the basis of our studies we wished to answer these questions: is it justified to perform routine thrombophilia screening of every patient before surgery; if not, is there a well

established patient group whose screening is advisable, and what would be the most efficient mode of prophylaxis in patients with thrombophilia.

PATIENTS AND METHODS

Thromboembolic prophylaxis for patients with total hip replacement surgery using UHF and physical methods

Using the data derived from 618 patients (385 women, aged 26 to 80 years, with a mean age of 61.2 years and 234 men, aged 27 to 83 years, with a mean age of 67.2 years), who underwent hip replacement surgery between 1984 and 1992 in the Department of Orthopaedic Surgery of the University of Debrecen, we evaluated the efficiency of thromboembolic prophylactic methods and the complications of pharmaceutical prophylaxis during the hospital treatment and at the orthopaedic follow up visits, which took place 3 months after the surgical procedure.

We provided pharmaceutical thromboembolic prophylaxis solely using sodium heparin (Heparibene Na, Ratiopharm), while calcium heparin (Heparibene Ca, Ratiopharm) was available a few years later. On the basis of the case histories, patients were classified into three (A, B, C) groups. UFH was used for pharmaceutical prophylaxis. Physical prophylaxis comprised of early mobilisation, remedial gymnastics and elastic banding applied on the lower extremities.

The 152 patients in **group A** had the history of diabetes mellitus (11 patients), severe heart disease (24 patients), neoplasm (4 patients), extensive varicose veins (46 patients), pathologic obesity (28 patients), previous DVT (31 patients), PE (2 patients) or both (6 patients).

8 patients received 3x1 ml (5000 U) sodium heparin 3 days before the surgery, while 144 patients received 2x0.3 ml (7500 U) calcium heparin subcutaneously. In order to prevent larger blood loss during surgery the administration of heparin was suspended 24 hours before surgery, then it was continued 4 hours after the procedure. Usually we only administered heparin until the 3rd or 4th postoperative day, then we continuously lowered the dose of heparin for 3-4 days, while started Syncumar administration with an increasing dose. Syncumar therapy was maintained for a half to one year, or longer in certain cases. Haemostasis parameters were continuously monitored, and heparin and Syncumar therapies were adjusted accordingly (APTT prolongation, baseline value + 5 secs, INR: around 2).

The 408 patients in **group B** had no history of thromboembolic diseases. 96 patients received 3x1 ml sodium heparin, while 312 patients received 2x0.3 ml calcium heparin for 10 days.

Haemostasis parameters were continuously monitored, and the dose of calcium heparin was adjusted according to the APTT prolongation. The desired target value was baseline APTT + 5 seconds of prolongation. If no manifest thromboembolic complication occurred during this period, pharmaceutical prophylaxis was ended. Early mobilisation was pushed in both groups, furthermore remedial gymnastics and the elastic banding of the lower extremities were recommended for 3 months.

58 patients in **group C** had the history of extremely high hypertension or cerebral haemorrhage, therefore in order to prevent haemorrhagic complications we did not employ pharmaceutical prophylaxis only physical methods.

Laboratory tests:

Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, haemoglobin, hematocrit, platelet count determinations were performed.

The tests were performed before surgery, immediately after surgery, and on the 2^{nd}, 5^{th}, 8^{th} postoperative days and if it became necessary.

Detection of thromboembolic complications:

DVT was detected by phlebography until 1990, then colour Doppler sonography (CD). PE was diagnosed using ventilation and perfusion scintigraphies.

Detection of haemorrhagic complications:

Perioperative blood loss and the development of haematomas were considered to adverse events to the medication used.

Evaluation of the efficacy of LMWH as a method of thromboembolic prophylaxis in the model of hip replacement surgery in animals

Our experiments were conducted on 20 hybrid dogs. While maintaining total anaesthesia (narcosis) we performed surgical exploration and manipulation of the appropriate body part which are usual during such operations in humans. The hip joint was disarticulated and the adducted and outwardly rotated position of the femur was maintained for 30 minutes as usual during such operations.

The animals were divided into two groups: **10 experimental dogs** received 100 AXa ICU/kilogram of body weight 4 hours before the operation and until the 3^{rd} postoperative day once a day, then from the 4^{th} postoperative day until the 10^{th} 150 AXa ICU/kilogram of body weight Fraxiparine (nadroparin Ca, Sanofi-Synthelabo) were administered once a day. **10 dogs in the control group** did not receive anticoagulant treatment.

Basic haemostasis tests were performed in both groups, starting from the day before the surgical procedure, until the 14th postoperative day. Perished animals were immediately dissected, while the rest of them were dissected on the 14th postoperative day, after employing overnarcosis.

Laboratory tests:

Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen levels were determined and Anti-Xa test was performed.

The dissection of experimental animals:

We looked for thrombi in the veins of the lesser pelvis and the lower limbs and sought for the signs of embolism in the lungs.

Comparing the efficacy of 10-day thromboembolic prophylaxis using UFH versus LMWH in patients, who underwent hip replacement surgery

We assessed the incidence of thromboembolic complications occurring despite prophylaxis employed for 10 days, using UFH in 312 patients between 1984 and 1992 (group I) and using LMWH in 100 patients between 1995 and 1996 (group II).

Group I comprised of 194 women (with a mean age of 60.8 years) and 118 men (with a mean age of 66.2), who received 7500 U of calcium heparin prophylaxis administered subcutaneously, twice a day.

Group II comprised of 57 women (aged between 31 and 83 years, with a mean age of 60.2 years) and 43 men (aged between 54 and 81 years, with a mean age of 63.4 years), who received 100 AXa ICU/kilogram of body weight Fraxiparine prophylaxis administered subcutaneously until the 3rd postoperative day, then 150 AXa ICU/kilogram of body weight prophylaxis until the 10th postoperative day.

Detection of thromboembolic complications:

DVT was detected by phlebography until 1990, then colour Doppler sonography (CD). PE was diagnosed using ventilation and perfusion scintigraphies.

The importance of pre- and postoperative colour Doppler sonography in the thromboembolic prophylaxis of hip replacement surgeries with 10-day long LMWH prophylaxis

We utilized the opportunities provided by colour Doppler sonography in order to detect asymptomatic deep vein thrombosis with incomplete obstruction of the vessel, thus

preventing the complete development of deep vein thrombosis with immediately introduced antithrombotic treatment.

We performed the prospective examination of 100 patients (61 women, 39 men, aged between 27 and 87 years, with a mean age of 59.6 years) in the **study group** who underwent hip replacement surgery between 1995 and 1996. We assessed diseases in the case histories, which rendered the patients susceptible for thromboembolic complications.

In order to provide thromboembolic prophylaxis for the patients, they received Fraxiparine in a dose of 100 AXa ICU/kilogram of body weight, administered subcutaneously 12 hours before the operation and once a day for three days after the intervention and 150 AXa ICU/kilogram of body weight between the 4^{th} and 10^{th} postoperative days.

The first colour Doppler sonography was performed 1-2 days before the surgery in order to assess the condition of the veins of the lower extremities. The efficiency of the antithrombotic treatment was assessed between the 5^{th} and 8^{th} postoperative days and 3 months after the surgery by examining the venous circulation of the lower extremities with colour Doppler sonography. If thromboembolic complication occurred, we followed up the thrombus and primarily in order to monitor the level of recanalisation, we performed colour Doppler sonographic examination several times.

The **control group** comprised of 100 patients who underwent similar operations and were treated with Fraxiparine in the same manner (57 women and 43 men, aged between 31 and 83 years, with a mean age of 61.2 years). We assessed the risk of the patients which rendered them susceptible for the development of thromboembolic complications.

Colour Doppler sonography was not routinely performed in this group, but only to verify the diagnosis of DVT if clinical symptoms occurred.

Comparing the efficacy of 10-day long and prolonged LMWH prophylactic schemes in patients who underwent knee replacement surgery using the routine colour Doppler sonography screening of the veins of the lower extremities

Group I comprised of 58 patients (43 women and 15 men with a mean age of 62.6 years) operated between 1995 and 1996, who received Fraxiparine prophylaxis for 10 days. A dose of 100 AXa ICU/kilogram of body weight was administered in the evening before the surgery, on the day of surgery and until the 3^{rd} postoperative day, then a dose of 150 AXa ICU/kilogram of bodyweight between the 4^{th} and 10^{th} postoperative day.

Group II comprised of 136 patients (101 women and 35 men with a mean age of 63.8 years) operated between 1997 and 2001, who received prolonged Fraxiparine prophylaxis. The same

dose of Fraxiparine was administered in the first 10 days as in Group I, furthermore prophylaxis was maintained with a dose of 100 AXa ICU/kilogram of body weight until the 35^{th}±7 postoperative day.

Colour Doppler sonography was performed on both lower extremities of every patient in both groups, 1-2 days before surgery, between day 5 and 8 after the surgery, and 1 month after the operation, for the preoperative assessment of the deep veins and for the early detection of an imminent thrombus.

Detection of abnormalities resulting in thrombophilia, which facilitate the development of thromboembolic complications in patients undergoing joint replacement surgery, in order to establish a more efficient method of prophylaxis

We conducted the prospective evaluation of 86 patients (aged between 26 and 89 years) undergoing hip and knee replacement surgeries between 1999 and 2001. We studied the correlations between the presence of thrombophilia and the occurrence of thromboembolic complications. On the basis of the case histories and medical documents available, we explored the thromboembolic history of the patients. All patients received pharmaceutical and mechanical prophylaxes during the perioperative period, in order to prevent thromboembolic complications. 72 patients received prolonged (35±5 days) LMWH prophylaxis. 14 patients, who had history of thromboembolic disease and therefore taking acenocoumarol tablets also received LMWH treatment in the perioperative period in order to prevent haemorrhagic complications, but later, usually from the 5^{th} to 7^{th} postoperative days, continuous acenocoumarol therapy was reintroduced.

The venous circulation of the lower extremities was assessed in every patient using colour Doppler sonography immediately before surgery, on the 5^{th} to 8^{th} postoperative days, and 1 month after the surgery. Colour Doppler sonography was performed several times in order to monitor the course of the complication in those patients, who developed DVT after the surgical procedure. PE occurring during the postoperative period was detected using ventilation and perfusion scintigraphies.

We used the recommended and revised scoring questionnaire for thrombosis screening, previously validated by Kümpel, to explore and evaluate the risk of thrombosis.

Scores under 6 posed low, scores between 6 and 10 meant moderate, while scores above 10 posed high thromboembolic risk.

During the follow up visit after one year, we assessed the thromboembolic events, which occurred while thromboembolic prophylaxis was employed and which occurred after the

conclusion of the prophylactic therapy. At that time laboratory tests were performed to detect thrombophilia, thus in addition to the routine haemostasis tests, fibrinogen, AT III, PC, PS and PL levels and activities were determined, furthermore APC rate measurement was performed and we screened for the presence of LA. Molecular genetic tests were used to detect factor V Leiden mutation and prothrombin G20210A polymorphism.

LABORATORY TEST METHODS:

Prothrombin time was determined using Innovin reagent, **activated partial thromboplastin time (APTT)** was determined with PTT–Automate reagent, **thrombin time** with Trombin time reagent, **fibrinogen** (reference range: 1.5-4.0 g/l) with Clauss assay, using fibrinogen reagent, **APC resistance** (reference range: > 2.0) with functional test REA-clot APC-R (V) reagent, **PL** (reference range: 80-120%) detection was performed using Stago reagent in a Stago Compact haemostasis analyzer (Diagnostica Stago, Asnieres, France).

AT III (reference range: 80-120%) was determined using Stachrom Antitrombin reagent and a chromogenic method, **PC** (reference range: 70-130%) was determined using Staclot Protein C reagent, **PS** (reference range: 65-140%) was determined using Staclot Protein S reagent, using a clotting method in the Stago Compact haemostasis analyzer (Diagnostica Stago, Asnieres, France). **Anti Xa test:** Factor X inhibition test for the quantitative determination of heparin using Stago reagent and a chromogenic method in the Stago Compact haemostasis analyzer (Diagnostica Stago, Asnieres, France).

The detection of **LA** was performed using LA sensitive APTT coagulation test.

Molecular genetic tests: **FV Leiden mutation** and **Prothrombin G20210A** were determined using blood samples with Na citrate anticoagulant. After DNA isolation (QIAamp DNA Blood Mini Kit, Qiagen, Hilden, Germany) real-time PCR and fluorescence resonance energy transfer (FRET) based detection, and melting point analysis were performed in a Roche Light Cycler instrument.

Hemoglobin concentration, hematocrit and platelet count were determined using a Technikon H-1 analyzer.

STATISTICAL ANALYSIS:

We used Statistica for Windows (Statsoft, Tulsa, USA) application software for the statistical analysis of our data. We calculated the mean values and the standard deviation of laboratory parameters. In these cases we utilized the two sample t-test to compare the data. χ^2-test was

used to compare non-parametric data. The differences were considered to be statistically significant if $p \leq 0.05$.

The incidence of thromboembolic complications (DVT and PE) of different severity were expressed in percent values within each group. The differences were considered to be statistically significant if $p \leq 0.05$.

During the analysis the number of complicated (DVT or PE) and uncomplicated cases were compared to each other and were expressed as ratios in both groups of experimental animals. We used the Wilcoxon test to compare the laboratory results.

RESULTS

Thromboembolic prophylaxis for patients with total hip replacement surgery using UHF and physical methods

We assessed that whether did we achieve 5 seconds of APTT prolongation or an INR value around 2.0 in our 618 patients: 384 women (with a mean age of 61.2 years) and 234 men (with a mean age of 67.2), who underwent hip replacement surgery between 1984 and 1992. Furthermore, we investigated thromboembolic and haemorrhagic complications and the ones caused by pharmaceutical prophylaxis.

All 8 patients in **Group A** received low dose sodium heparin treatment for 3 days after the surgery and the desired 5 seconds of APTT prolongation was achieved in all of them by the 2^{nd} postoperative day. Switching to Syncumar (acenocoumarol) therapy was started on the 4^{th} postoperative day and every patient's INR value was around 2.0 by the 8^{th} postoperative day. From that time, these patients were on continuous Syncumar therapy with regular laboratory follow-ups. Neither thromboembolic nor haemorrhagic complications did occur during the studied period.

144 patients received calcium heparin for 3 days and 112 among these reached the desired 5 seconds of APTT prolongation by the 2^{nd} postoperative day. Switching to Syncumar therapy was started from the 4^{th} postoperative day, and by the 8^{th} postoperative day 96 patients reached an INR value around 2.0, while 48 patients reached an INR value around 1.5 respectively. DVT was detected in 4 patients within 8 days, and among them 1 patient had PE with fatal outcome. 10 patients were diagnosed to have DVT after the 8-day period, with 2 of them having PE but with no fatal outcome. An INR value around only 1.5 was reached in these patients, which turned out to be insufficient to prevent thromboembolic complications. No haemorrhagic complications requiring treatment were observed.

All 408 patients in **Groub B** received thromboembolic prophylaxis for 10 days following the surgical procedure, 96 among them received sodium heparin while 312 received calcium heparin therapy. The desired 5 second-long APTT prolongation was achieved in 68 patients in the sodium heparin group, while in 239 patients in the calcium heparin group. Neither DVT nor PE did develop in either group within 8 days. After 8 days, DVT occurred in 6 patients of the sodium heparin group, while 16 DVT and 1 PE occurred in the calcium heparin group. Regarding those patients, who had an APTT prolongation of ≤4 seconds, 4 DVT and 1 PE occurred in the sodium heparin group, while 14 DVT and 1 PE in the calcium heparin group. After 8 days, DVT occurred in 4 patients of the sodium heparin group, while 12 DVT and 3 PE occurred in the calcium heparin group.

2 haemorrhagic complications occurred due to sodium heparin overdose, which were corrected after administering protamine sulphate and fresh blood transfusion.

No haemorrhagic complications occurred in the calcium heparin group, but heparin induced thrombocytopenia occurred due to the increased dose heparin therapy in one female patient suffering from DVT and PE. Therefore we switched to Syncumar therapy, which resulted in the very rare complication of acenocoumarol associated dermal necrosis. The patient received Aspisol, Trental and Antithrombin III therapies and 2x200 ml/day were administered. Her thrombocytopenia regressed and the necrotic areas of the leg were amputated and the stump healed well.

58 patients in **Group C** did not receive pharmaceutical thromboembolic prophylaxis. Neither haemorrhagic nor thromboembolic complications did occur within 8 days. After 8 days 9 patients had DVT and 2 of them had PE as well, while no haemorrhagic complications were observed.

Evaluation of the efficacy of LMWH as a method of thromboembolic prophylaxis in the model of hip replacement surgery in animals

Laboratory test results

In the group treated with LMWH (10 animals) the level of Factor Xa inhibition between the 1st and 5th postoperative days was 0.2-0.3 AXa ICU/ml, while between the 6th and 11th postoperative days it was measured to be 0.3-0.4 AXa ICU/ml. Thromboembolic prophylaxis was concluded on the 10th postoperative day, thus the degree of Factor Xa inhibition gradually returned to zero by the 14th postoperative day.

Significant changes in fibrinogen levels ($p<0.05$) were observed in 5 animals in the control group. Significant thrombocytopenia ($p=0.00086$) was observed in 1 dog.

Dissection results:

Thrombi in the lower extremities were detected in those 5 dogs of the control group, whose fibrinogen levels were significantly elevated. One of these five animals died of PE on the 7th postoperative day, and it also had significant thrombocytopenia as well.

Comparing the efficacy of 10-day-long thromboembolic prophylaxis using UFH versus LMWH in patients, who underwent hip replacement surgery

Group I comprised of (312 patients) 194 women (with a mean age of 60.8 years) and 118 men (with a mean age of 66.2), who received 7500 U of calcium heparin prophylaxis administered subcutaneously, twice a day.

Group II comprised of (100 patients) 57 women (with a mean age of 60.2 years) and 43 men (with a mean age of 63.4 years), who received 100 AXa ICU/kilograms of bodyweight Fraxiparine prophylaxis administered subcutaneously until the 3rd postoperative day, then 150 AXa ICU/kilograms of bodyweight prophylaxis until the 10th postoperative day.

We registered only the thromboembolic complications accompanied by clinical symptoms.

During the prophylaxis period, 14 patients (4.48%) in the UFH group had DVT, 1 patient (0.32%) had PE and 2 patients (0.64%) had haemorrhagic complications requiring surgical intervention.

9 patients (9.0%) had DVT in the LMWH group, but neither PE nor haemorrhagic complications requiring surgical intervention did occur in this group.

After the conclusion of the prophylactic therapy 28 patients (8.97%) in the UFH group had DVT and 4 of them (1.28%) had PE, while in the LMWH group 3 patients (3.0%) had DVT and 2 (2.0%) PE. Haemorrhagic complications did not occur in either group. Thromboembolic complications occurred between the 25th and 30th postoperative days.

The importance of pre- and postoperative colour Doppler sonography in the thromboembolic prophylaxis of hip replacement surgeries with 10-day long LMWH prophylaxis

Colour Doppler sonographic examination of the lower extremities was performed in 100 patients (with a mean age of 59.6 years), who underwent hip replacement surgery. Between the 5th and 8th postoperative days we found thrombi partially occluding the veins of 4 patients. In these four cases, we increased the dose of Fraxiparine to therapeutic level and from then on these abnormalities were treated as DVT. Neither total occlusion nor pulmonary embolism did occur in either case.

Colour Doppler sonography was performed in patients of the control group, whose clinical picture indicated DVT. 9 cases (9%) of DVT were detected between the 5th and 8th postoperative days (with χ2-test $p<0.01$ compared to the study group, significant), and 1 case of DVT was detected on the 25th, 27th, 30th postoperative days each (3%) (with χ2-test $p=0.08$ compared to the study group). Pulmonary embolism was detected on the 28th and 31st postoperative days, 1 case on each days (25). One was verified by CT scan, while the other was of fatal outcome. The source of embolism was not found in either case. Regarding the incidence of pulmonary embolism we did not find significant difference compared to the study group using the χ2-test ($p=0.15$).

Comparing the efficacy of 10-day long and prolonged LMWH prophylactic schemes in patients who underwent knee replacement surgery using the routine colour Doppler sonographic screening of the veins of the lower extremities

58 patients (with a mean age of 62.6 years), who were operated between 1995 and 1996 received Fraxiparine prophylaxis for 10 days. The colour Doppler sonography of both lower extremities was performed at 1-2 days before the surgical procedure, between the 5th and 8th postoperative days, and 1 month after the surgery. Between the 5th and 8th postoperative days we found thrombi partially occluding the vein of 1 patient (1.7%). The dose of Fraxiparine was increased to therapeutic level and from then on these abnormalities were treated as DVT. No partial thrombus was detected 1 month after the surgery, however clinically evident DVT occurred in two patients (3.4%) on the 14th postoperative day in the first one and on the 25th postoperative day in the second one, as colour Doppler sonography verified the total occlusion of the vessels. Due to the effect of the antithrombotic therapy employed these patients completely recovered and no complications occurred.

Prolonged Fraxiparine prophylaxis was employed in 136 patients. Partial thrombi were detected in 8 cases (5.9%) between the 5th and 8th postoperative days. Partial thrombi were detected in 3 patients (2.2%) 1 month after the surgery. In this group we did not find thrombi, which would totally occlude the lumen of the affected vein.

The distribution of the different complications in the two groups was assessed by χ^2-test for homogeneity. According to the result of this test, there was no significant difference between the two groups, neither regarding the period of 1-2 days before the surgery, nor during the 5th to 8th postoperative day period ($p>0.05$). Based on the examinations performed 1 month after the surgery the difference in the distribution of complications between the two groups was also not significant, however this was the most remarkable difference between the two groups.

Haemorrhagic complications requiring surgical exploration occurred in 1 instance in both groups, while minor bleeding occurred in 17.2% and 15.5% respectively. No significant difference regarding the haemorrhagic complications was observed between the two groups ($p>0.05$).

Detection of abnormalities resulting in thrombophilia, which facilitate the development of thromboembolic complications in patients undergoing joint replacement surgery, in order to establish a more efficient method of prophylaxis

We studied a total of 86 patients (with ages between 26 and 89 years), who underwent knee or hip replacement surgery. 33 patients (38%) among them had thrombotic or thromboembolic event.

Age and gender were not predictive factors regarding the occurrence of thromboembolic complications. The risk score for thrombosis was significantly higher ($p<0.001$) in symptomatic patients, which indicates that this simple estimator scale is suitable for the preoperative assessment of thromboembolic risk. Significant differences were found between the two groups (symptomatic and asymptomatic) regarding the presence of LA ($p=0.02$), the APC ratio and APC resistance values ($p<0.02$), factor V Leiden mutation ($p<0.02$) and regarding the mutation rate of the prothrombin gene ($p<0.05$).

If haemostasis and genetic variables were paired (PS + Leiden mutation, PS + LA) the incidence of thromboembolic complication did not increase, however, we must note that more combined gene mutations and more patients with thrombophilia were present in the symptomatic group.

During the next analysis we studied that when did the thrombotic/thromboembolic event occur and whether was there correlation between the postoperative complications and the thrombophilia detected.

Preoperative deep vein thrombosis occurred in 17.4% of the total patient population, while the joint incidence of DVT and pulmonary embolism was 4.6%.

The incidence of postoperative thrombosis and thromboembolic events was 20.7%. It must be noted, that these 18 cases added up the 55% of all the thromboembolic events (n=33) occurring any time throughout the observed periods. The most common postoperative thrombotic complications were deep vein thromboses, which occurred while thromboprophylactic therapy was employed and even afterwards. Thrombophilia could have been detected in almost all of the postoperative complicated cases and the prevalence of

genetic defects was also relatively high. Thus, we compared the incidence of thrombotic complications in the acenocoumarol and in the LMWH prophylaxis groups.
No thrombotic events were registered at all during the postoperative period in the acenocoumarol group, while 4 DVT and 1 case of pulmonary embolism occurred in the LMWH group during the prophylaxis. It is also unquestionable, that thrombotic/thromboembolic complications were more common in the LMWH group after the conclusion of prophylactic therapy. If we compared the haemostasis and genetic parameters of the acenocoumarol and LMWH groups, we only found differences in the prevalence of lupus anticoagulant (1/14 vs. 7/19, $p<0.05$) and the prevalence of combined gene mutations (4/14 vs. 3/19, $p<0.05$).

DISCUSSION

Thromboembolic prophylaxis for patients with total hip replacement surgery using UHF and physical methods

Hip replacement surgical procedures were started in 1984 and we used low dose heparin treatment i.e. 3x5000 U sodium heparin for thromboembolic prophylaxis until 1987, then adjusted doses of calcium heparin until 1992. A total of 618 patients underwent hip replacement surgery during this period. Based on their case histories patients were divided into A, B and C groups.

Patients in **Group A** (152 patients) had history of diseases, which rendered them susceptible for thromboembolic complications, therefore they received Syncumar (acenocoumarol) therapy before the surgical procedure. They received either sodium or calcium heparin in the perioperative period to prevent the haemorrhagic complications, then Syncumar therapy was re-adjusted and maintained for a half to one year. DVT occurred in 14 patients (9.21%), while PE occurred in 3 patients (1.97%) and 1 (0.65%) of these was of fatal outcome. Thromboembolic complications occurred in those patients only, whose INR value was only around 1.5 with the Syncumar therapy employed.

In case of Syncumar therapy, an INR value of around 2.0 is necessary to achieve a significant reduction in the incidence of thromboembolic complications (DVT: 9.21%, PE: 1.97%, fatal PE: 0.65%) and to prevent haemorrhagic complications. In the case of INR being $\leq$1,5 the incidence of thromboembolic complications significantly increases (DVT: 29.1%, PE: 6.25%, fatal PE: 2.08%). Significant differences were found between the two groups

($p<0.001$). The results were marginally better than of those who didn't receive thromboembolic prophylaxis.

408 patients in **Group B** received low dose sodium heparin, or adjusted dose of calcium heparin prophylaxis for 10 days. Our objective was to achieve an APTT prolongation of 5 seconds compared to the baseline value. We achieved this goal in 68 patients out of 96 (70.8%) in the **sodium heparin group.** During the prophylactic treatment severe haemorrhagic complications occurred in two patients (2.08%) due to sodium heparin overdose and DVT occurred in 6 patients (6.25%) after the prophylaxis was concluded. In those patients, whose APTT prolongation was ≤4 during the prophylaxis and after its conclusion 4 cases (8.33%) of DVT and 1 (2.08%) case of PE developed in both instances (during and after prophylaxis).

Heparin was first marketed in 1987 in the formulation of a calcium based salt, which had the tremendous benefit that it required two subcutaneous administrations of the drug per day and 0.2 ml of the active substance was equivalent with 1 ml of sodium heparin. That was the reason behind switching to calcium heparin prophylaxis.

Those patients of the **calcium heparin** group, who achieved a 5-second long APTT prolongation had DVT (16 patients, 5.12%) and PE (1 patient, 0.32%) only after the conclusion of the prophylaxis.

DVT (14 patients, 4.48%) occurred during prophylaxis in those patients only whose APTT prolongation was only ≤4 seconds. After the prophylaxis, we detected 12 cases (3.84%) of DVT and 3 cases (0.96%) of PE. No haemorrhagic complications occurred. HIT occurred in one female patient receiving calcium heparin prophylaxis. The most probable underlying cause was the presence of heparin dependent IgG type antibodies as they facilitate platelet aggregation *in vivo* and *in vitro* as well. In this case we could not switch the UFH treatment to LMWH as it was recommended by scientific literature, because the Fraxiparine and Fragmin products available triggered *in vitro* platelet aggregation as well. That is why our patient received Syncumar therapy. The rare complication of acenocoumarol associated dermal necrosis occurred as a side effect of the Syncumar treatment. Acenocoumarol associated dermal necrosis occurs in PC deficient patients, which is more frequent in women. In addition to PC deficiency, DVT, PS deficiency and ATIII deficiency are also predisposing factors to acenocoumarol associated dermal necrosis. Gangrene occurred due to the acenocoumarol associated necrosis, therefore we performed necrectomy and the amputation of Charcot's joint. Later the wound was covered during a dermal plastic procedure.

The patient's limbs became healed and she can maintain a normal every day life wearing orthopaedic shoes.

58 patients of **Group C** only received physical prophylaxis since their primary disease rendered them susceptible for haemorrhagic complications if pharmaceutical prophylaxis would have been used. DVT occurred in 9 patients (15.5%) and PE occurred in 2 patients (3.44%). Today this method is considered to be inappropriate and we have provided pharmaceutical prophylaxis for every patient since the marketing of LMWH products.

Adjusted dose heparin is more favourable to low dose heparin, however there was no significant difference in the incidence of thromboembolic complications between the two groups, but haemorrhagic complications occurred in the low dose group only. While employing UFH, one most bear in mind the potential risk of HIT and HITT as well.

Evaluation of the efficacy of LMWH as a method of thromboembolic prophylaxis in the model of hip replacement surgery in animals

No clinical symptoms indicating thromboembolic complication were detected in the experimental animal group during the treatment. Dissection revealed neither thrombi in the veins, nor embolism in the lungs in either dogs. However, regarding the control group, DVT was detected in 5 animals (50%) and PE in 1 dog (10%), which perished on the 7^{th} postoperative day. We concluded that there were significant differences between the two groups regarding the incidences of DVT and PE. Our study further verified the efficacy of LMWH products in the prevention of thromboembolic complications.

To sum it up, the following conclusion can be drawn from our animal experiments: the measurement of haemostasis parameters and the level of fibrinogen does not provide adequate information regarding the development of thromboembolic complications in subjects undergoing joint replacement surgery. The presence of thrombocytopenia is not specific to DVT and PE. If a 0.3-0.4 AXa ICU/ml FXa inhibition is maintained, thromboembolic complications can be prevented, however we do not recommend its routine use as screening due to it costs.

Comparing the efficacy of 10-day-long thromboembolic prophylaxis using UFH versus LMWH in patients, who underwent hip replacement surgery

When comparing the results of prophylaxis maintained with UFH for 10 days in 312 patients, who underwent hip replacement surgery between 1984 and 1992 (Group I), and with LMWH for 10 days in 100 patients, who underwent hip replacement surgery between 1995 and 1996

(Group II), we found that fewer DVT (4.48%) occurred in the UFH group than in the LMWH group (9%). Our results differ from that of other investigators, who found greater incidence of DVT in the group receiving IFG prophylaxis. A possible explanation to this difference is that we only registered DVTs, which were accompanied by clinical symptoms, thus other DVTs with more discrete symptoms might have remained undetected. In the case of a proximal DVT, patients have a 35% risk of developing pulmonary embolism. Only a quarter of DVTs occurring despite LMWH prophylaxis can be classified as proximal, which significantly lowers the risk of developing a clinically manifest PE. This was verified in a study conducted by Leyvraz et al. in 28 European countries. The incidence of DVTs was similar to those data mentioned in the scientific literature and decreased by 75% in Group II (1%) compared to Group I (3.38%). 1 case (0.32%) of PE occurred only in Group I, which seems to support the previous observations in the literature that PE rather develops after proximal DVTs.

Significant difference ($p<0.04$) was found between the two groups in the incidence of MVT after the conclusion of the prophylactic therapy. After the conclusion of the prophylactic therapy, between the 25th and 30th postoperative days, DVT occurred in 8.97% of the patients in Group I and in 3% of the patients in Group II. PE occurred in 1.28% and 2% respectively. We concluded that 10 days of LWMH prophylaxis is insufficient to prevent the occurence of thromboembolic complications.

Based on the similar results of other investigators and considering their therapeutic recommendations as well, started in 1997, we were the first in Hungary to introduce 35+7 days of prolonged LMWH prophylaxis in every patient undergoing joint replacement surgery.

The importance of pre- and postoperative colour Doppler sonography in the thromboembolic prophylaxis of hip replacement surgeries with 10-day long LMWH prophylaxis

Colour Doppler sonography was performed in 100 patients undergoing hip replacement surgery and who had 10-day long LMWH prophylaxis (with a mean age of 59.6 years). The sonographic examinations were performed on both lower extremities 1-2 days before the surgical procedure, between the 5th and 8th postoperative days and 1-3 months after the surgery. Another group of 100 patients undergoing hip replacement surgery (with a mean age of 61.2 years) with the same prophylactic therapy had colour Doppler sonographic examinations but only to verify the diagnosis of DVT.

We found thrombi partially occluding the affected veins in 4 patients of the colour Doppler group, between the 5th and 8th postoperative days. No PE occurred. 12 cases of DVT were

detected in the control group. 9 out of these were detected between the 5th and 8th postoperative days, while 3 of them were detected on the 24th, 26th and 30th postoperative days respectively. 2 incidences of PE were detected on the 28th and 32nd postoperative days respectively. One of them was of fatal outcome.

We concluded that the easy, non-invasive colour Doppler sonography has an outstanding importance in the prevention of thromboembolic complications, since they can detect those partially occlusive thrombi, which do not have clinical symptoms quite early,
and the appropriately initiated therapy can prevent the total occlusion of the deep veins and the consequent pulmonary embolism.

DVTs after surgery are most common between the 5th and 8th, furthermore between the 25th and 30th postoperative days. The risk for PE is the highest between 1-3 months after the surgical procedures.

These studies clearly demonstrate that thromboembolic complications may only be prevented by using prolonged prophylactic therapy.

Comparing the efficacy of 10-day long and prolonged LMWH prophylactic schemes in patients who underwent knee replacement surgery using the routine colour Doppler sonographic screening of the veins of the lower extremities

58 patients (Group I, with a mean age of 62.6 years) received Fraxiparine prophylaxis for 10 days. 136 patients (Group II, with a mean age of 63.8 years) received prolonged LMWH prophylaxis. The colour Doppler sonography of both lower extremities was performed in both groups at 1-2 days before the surgical procedure, between the 5th and 8th postoperative days, and at 1 month after the surgery.

Between the 5th and 8th postoperative days partial thrombi were detected in 1.7% of the patients of Group I, while in 5.9% of the patients of Group II. After the conclusion of prophylaxis, we detected thrombi causing total occlusion in two patients (3.4%) of Group I on postoperative days 14th and 25th respectively. The development of DVT was explained by the early conclusion of the prophylactic therapy.

Partial thrombi were found with colour Doppler sonography in 3 patients (2.2%) of Group II, 1 month after the surgery. These thromboses became healed due to the effect of the antithrombotic therapy employed.

Based on data from the scientific literature, the mean interval until the occurrence of thromboembolic complications after knee replacement surgery is 9.7 days. Therefore certain

investigators find 10 days of prophylaxis to be sufficient in patients undergoing knee replacement surgery. On the contrary, some other authors, including ourselves, recommend prolonged prophylaxis in this patient group as well in order to ensure safety.

Detection of abnormalities resulting in thrombophilia, which facilitate the development of thromboembolic complications in patients undergoing joint replacement surgery, in order to establish a more efficient method of prophylaxis

The objective of this prospective, descriptive study was to determine that what kind of haemostatic and genetic parameters render patients susceptible to developing thromboembolic complications. The reason for this study was that the incidence of thromboembolic complications in patients undergoing joint replacement surgery is still 6-10%, despite the modern LMWH prophylaxis employed.

Our results were similar to the ones published by other authors previously, since the incidence of postoperative thromboembolic complications in our patients was 5.7% 4 DVT (4.6%) and 1 PE (1.1%) despite LMWH prophylaxis. However, we must emphasize that all cases occurred in thrombophilic patients. Therefore, we performed further analysis to verify our assumption that the majority of postoperative thromboembolic events can be associated to thrombophilia and combined genetic defects. Thrombophilia was more frequent in our symptomatic patients (18/33), compared to the asymptomatic group, where this ratio was 12/53 ($p \leq 0.01$). In addition, all patients with thrombotic complications were diagnosed to be thrombophilic.

If we would like to study the factors predisposing to thrombophilia in detail, we have to analyze a few important factors like AT-III deficiency, protein C activity, protein S and plasminogen activity, APC resistance, factor V Leiden mutation and the presence of lupus anticoagulant. Protein S deficiency is a rare thrombophilic factor and was present in 14 cases among our patients. However, we must note, that 4 of these patients had thromboembolic events and all of these patients proved to have combined thrombophilia; decreased PS + factor V Leiden mutation. Factor V Leiden mutation was likely to be the cause of the thrombotic events detected in these 4 patients. Significant differences were demonstrated between the symptomatic (n=8) and asymptomatic (n=3) patients groups, regarding the presence of lupus anticoagulant (LA). Factor V Leiden mutation is one of the thrombophilic factors of outmost importance. Heteroallele factor V Leiden mutations were detected in 11 patients. This is somewhat higher than the previously published values. The fact that the prevalence of factor V Leiden mutation was 24.2% in the symptomatic group and 5.6% in the asymptomatic group

($p \leq 0,01$) – which corresponds well to the previously published results in scientific literature - underlines the clinical importance of this mutation.

From the genetic factors we assessed, prothrombin G20210A mutation was present in 3.4% (n=3) of the cases. These were all symptomatic patients. Based on our analysis it is evident that isolated thrombophilic factors are rarely the cause of thromboembolic complications as combined thrombophilias and genetic defects are the causes to be accounted for regarding the majority of these complications. The prevalence of combined genetic defects was 21.2% in the symptomatic group, while it was 1.8% in the asymptomatic group ($p \leq 0.02$). Similarly to our previous results, the prevalence of combined thrombophilias was higher in the symptomatic group (54.5%) compared to the asymptomatic group (22.6%, $p \leq 0.01$).

These results might raise the question that whether it is necessary to perform routine screening tests for congenital thrombophilias before all orthopaedic joint replacement surgeries. According to our opinion screening tests are reasonable if the patient has a history of thromboembolic event, in the case of cumulative family history and if the patient has 15 points or more in the score system predicting thrombosis risk.

What kind of treatment shall be employed in thrombophilia positive cases?

In our studies we found acenocoumarol therapy to be more safe in patients with thrombophilia compared to postoperative LMWH prophylaxis. Those patients, who have history of thromboembolic events and are thrombophilic we recommend individualized evaluation and therapy. In the cases of combined defects, we find it necessary to maintain continuous anticoagulant therapy. In order to provide an evidence-based answer to this question, a randomised study with larger patient population is required.

SUMMARY – NEW RESULTS

Thrombosis prophylaxis is necessary in patients undergoing hip or knee replacement surgery.

1. UHF was the only prophylactic method available for us until 1995. The adjusted dose heparin prophylaxis was more efficient and safe compared to the low dose heparin prophylaxis. Haemorrhagic complications and rarely HIT and HITT might occur while using UFH. We concluded that if switching to Syncumar (acenocoumarol) therapy is necessary in a patient, who underwent hip or knee replacement surgery, an INR value around 2.0 shall be achieved in order to avoid bleeding complications, while maintaining appropriate thromboembolic prevention.

2. During our animal experiments using a hip replacement surgery model we determined that with a 0.3-0.4 AXa ICU/ml FXa inhibition achieved, thromboembolic complications can be prevented. The significant elevation of fibrinogen levels marks the development of a thrombus under experimental conditions, however our data cannot verify this in the clinical practice.

3. We managed to decrease the incidence of thromboembolic complications with 10 days of LMWH prophylaxis, however new complications occurred between the 25^{th} and 28^{th} postoperative days, due to gradually increasing coagulability. Therefore in 1997, we were the first in Hungary to introduce the so called prolonged, 35± 7 days of LMWH prophylaxis.

4. We concluded that the easy, non-invasive and cheap colour Doppler sonography screening examination has an outstanding importance, since it can detect clinically asymptomatic, partially occlusive thrombi, thus the antithrombotic treatment introduced in time can prevent the total occlusion of the deep veins and the consequent pulmonary embolism.

5. Thrombophilia is the frequent underlying cause of thromboembolic complications occurring despite modern thromboembolic prophylactic therapy. Based on our studies, we are on the opinion, that thrombophilia screening tests before joint replacement surgery are reasonable only if the patient has a history of thromboembolic event, has a cumulative family history and if the patient has 15 points or more in the score system predicting thrombosis risk.

6. Acenocoumarol treatment was proven to be safer the prolonged prophylaxis in those patients, who had the history thromboembolic events and were thrombophilic at the same time. According to our opinion, in the case of thrombophilic patients, prophylactic therapy shall be established on individualized assessment and consideration.

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