

THE EFFICIENCY OF LOW MOLECULAR WEIGHT HEPARINS IN THE PROPHYLAXIS OF VENOUS THROMBOEMBOLIC COMPLICATIONS IN GENERAL SURGERY

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Abstract

Deep venous thrombosis (DVT), with its possible serious consequences (pulmonary thromboembolism- PTE- which can lead to death) often influence the morbidity and mortality of surgical interventions, especially in the field of general surgery, traumatology, orthopedy, gynecology and urology.

In a retrospective study on 3875 patients hospitalized and operated in the Surgery Clinic of "St. Pantelimon" Emergency Hospital, Bucharest, Romania, during 2002-2006, patients that benefited of thromboprophylaxis with low molecular weight heparins (LMWH), there were analysed the risk factors for DVT and PTE, the efficiency of the therapy and hemorrhagic complications. LMWH represent safe thromboprophylactic agents, the postop hemorrhagic complications of the treated patients being minor, benefits exceeding risks. The rate of hemorrhagic complications was 2.04%, most of them being approached in the conservative manner (97.5% of them). Only 2 cases of haemoperitoneum needed surgical interventions, which represents 0.5% in a thousand of patients treated with LMWH. On the other hand, the rate of thrombotic complications lowered under 1% (0.92%) and death by PTE occurred in 3 cases (0.077%). From the patients submitted to prophylaxis with LMWH, who nevertheless developed thromboses (inefficient thromboprophylaxis), 44.44% were patients with neoplastic diseases, an association which is statistically significant. Thus, neoplastic disease represents both a risk factor and an important factor for the inefficiency of the thromboprophylaxis with LMWH.

Rezumat

Tromboza venoasă profundă (TVP) și complicațiile sale (tromboembolismul pulmonar-TEP- ce poate conduce la deces) reprezintă evenimente care adesea cresc morbiditatea și mortalitatea unor intervenții chirurgicale, în special în domeniul chirurgiei generale, traumatologiei, ortopediei, ginecologiei și urologiei.

Într-un studiu retrospectiv pe 3875 pacienți internați și operați în Clinica de Chirurgie a Spitalului Clinic de Urgență "Sf. Pantelimon" din București, în perioada 2002-2006, pacienți care au primit tromboprofilactic heparine cu greutate moleculară mică (HGMM), s-au analizat factorii de risc pentru TVP/TEP, eficiența profilactică și complicațiile ei hemoragice. Tromboprofilaxia cu HGMM reprezintă o metodă sigură de tratament, complicațiile hemoragice postoperatorii la pacienții tratați fiind minore,

beneficiile fiind mai mari decât riscurile. Rata complicațiilor hemoragice a fost de 2,04%. Doar 2 cazuri de hemoperitoneu au necesitat reintervenții chirurgicale, ceea ce reprezintă doar 0,5% dintre pacienții tratați cu HGMM. Pe de altă parte, rata complicațiilor trombotice a scăzut sub pragul de 1% (0,92%), iar decesul prin TEP s-a înregistrat doar pentru 3 pacienți (0,077%). Dintre pacienții supuși tromboprofilaxiei cu HGMM care au dezvoltat totuși tromboze (tromboprofilaxie ineficientă), 44,44% erau pacienți cu boală neoplazică, asocieră semnificativă statistic ($p < 0,01$). Astfel, boala neoplazică reprezintă un factor de risc, dar și un important factor de ineficiență al tromboprofilaxiei cu HGMM.

Keywords: thromboprophylaxis, deep venous thrombosis (DVT), pulmonary thromboembolism (PTE), low molecular weight heparins (LMWH)

Introduction

Venous thrombosis can be developed in different anatomic regions, having different clinical and treatment particularities. There are a few main types of venous thrombosis: venous thrombosis of the superficial veins of the upper limb, venous thrombosis of the deep venous axis of the upper limb (brachial vein, axillary vein, subclavian, brachiocefalic venous trunk), thrombosis of the deep venous system of the lower limb. Deep venous thrombosis (DVT) occurs especially after extended immobilization in bed (orthopedic surgical interventions), in young people but especially in old people. DVT is a dangerous disease, because it is caused by a detachment of a thrombus from the peripheral venous system, that migrates to the pulmonary arteries or their ramifications and it totally or partially blocks them. This complication is called pulmonary embolism and it is a medical emergency. Massive pulmonary embolism can be fatal in very short time (minutes) and it is the most frequent complication of the deep venous thrombosis. Venous thrombosis is caused by injuring the internal surface of the vein, for instance in accidents, operations, inflammations or immune diseases, in lack of movement (for instance after operations or fractures, in case of administration of oral contraceptives or diuretics, in dehydration and also in case of cancer).

Prevention of venous thromboembolic complications in general surgery represents nowadays a constant preoccupation and it should be used if the patient develops one or more risk factors that impose rigorous application of thromboprophylaxis measures. The main risk factors involved in the pathogenesis of the venous thrombosis (VT) were brought together since 1845 under the name of "Virchow triad" (represented by lesions of the venous wall, hypercoagulability of the blood and venous stasis). The risk factors of deep venous thrombosis (DVT) were recently organised in extrinsic and intrinsic factors [1,2]. Although these risk factors are well known, sometimes easily but, also, sometimes extremely difficult to be

clinically diagnosed, although there are of multiple paraclinic investigations available on a large scale, venous thromboembolism represents a medical emergency, whose evolution is frequently dramatic. Aside of the unfavourable impact on the patient's functional and vital prognosis conferred by the pulmonay embolism, the deep venous thrombosis is followed by the appearance on medium and long term of the postthrombotic syndrome, with negative impact on the quality of life.

In surgical wards (orthopedy, gynecology and general surgery wards hold the "supremacy" regarding the number of thrombotic complications), prophylaxis measures are imposed in patients with risk. Among these there can be mentioned: precocious mobilisation, elastic stockings, good hydration, as well as pharmacoprophylaxis with antiplatelet drugs and low molecular weight heparins (LMWH). The last ones are nevertheless more often chosen as prophylactic treatment. Still, even maximal thromboprophylaxis is applied, in accordance with clinical recommendations in force (including LMWH), does not exclude this type of complications. This is why deep venous thrombosis continues to arouse a real interest from the therapy point of view, which is still controversial.

Material and Methods

The accomplished study was a retrospective one (Jan 1st 2002- Dec 31st 2006), with the collection of data from available medical documents from "St. Pantelimon" Emergency Hospital, Bucharest, Romania: observation sheets of the patients, endoscopic (colonoscopic) bulletins, histopathological bulletins, books of surgical protocols. The method that was used in this work is the observational study (non-experimental), of descriptive type.

Criteria of inclusion

In the study group, there were included patients aged over 20, with complex middle and major surgeries, for benign conditions, but especially malignant conditions with associated medical pathology, vascular injuries as well as patients with minor risk. There were excluded patients under 20 years old, the ones who were not operated (except the ones with DVT priors), with low risk, coagulation problems, recent acute hemorrhage (except the ones considered for haemostasis), malignant high blood pressure, severe hepatic disease, acute or cronic renal failure with coagulation problems, severe acute pancreatitis, allergy to heparins, recent heart attack (under 3 months), pregnancy or lactation.

There were observed: the distribution of the patients acoording to age and sex, the presence and evaluation of extrinsec factors of DVT and their

inclusion in a risk class, monitoring of postop evolution and efficiency of heparin thromboprophylaxis by evaluation of DVT incidence, necessary paraclinical investigations including venous Doppler ultrasound, adverse reactions to the anticoagulant treatment, efficiency of thromboprophylaxis by evaluation of DVT incidence, number of deaths by pulmonary embolism. From over 15,000 (15,653) patients that were hospitalized in the Surgery Clinic of „St. Pantelimon” Hospital in Bucharest during the period 2002-2006, almost 66% were operated (in the classic manner a number of 7350 cases, laparoscopic a number of 2150 cases). For 40% of these –a number of 3875 cases, the risk factors were identified and heparin thromboprophylaxis was imposed.

According to the number of the involved risk factors, the patients were grouped in classes of gravity, established after Oakes [3]:

- major and high risk (risk coefficient >10) - there were included 1860 (48%) patients,
- medium risk (risk coefficient 2-9) - 1300 (33.55%) patients.
- low risk (risk coefficient less <2)- 715 (18.45%) patients.

All patients with risk, selected before the surgeries, no matter the gravity, were included in the protocol of heparin thromboprophylaxis established 1-2 hours before surgeries, using LMWH administrated subcutaneously, the rythm of administration being imposed by the risk class and the type of LMWH used. The treatment was administred for 5-7 days, and in cases of immobilisation and prolonged hospitalization, the duration of heparinotherapy was adequately longer.

Results and Discussions

Sex, as a risk factor, showed a higher incidence in women (69.33%) than in men (30.66%). (fig.1)

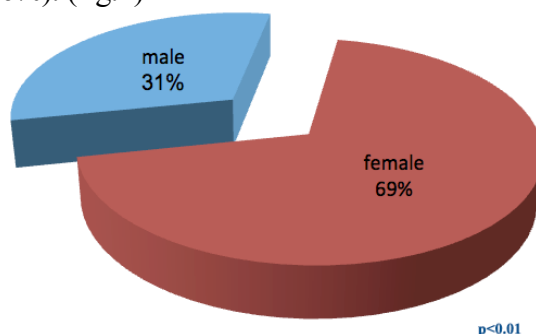


Figure 1

The incidence of risk factors in women and men

The statistically significant difference ($p < 0,01$) and explained by the existence of thromboembolic risk factors more numerous in women (venous insufficiency of lower limbs, obesity, interventions in genital area, hormonal treatments of substitution or contraceptives, identified also in our casuistry-table I)

Table I
The evaluation of the general risk factors

Risk factors	No. of observations
Obesity	2053 patients
Diabetes (mellitus)	1162 patients
Age over 40	2518 patients
Smoking	1550 patients
Neoplastic disease	865 patients
Varicose disease	135 patients
Systemic infections	250 patients
Congestive heart failure	321 patients
Prolongued immobilization	271 patients
Hormonal therapy	300 patients
Chronic obstructive pulmonary disease	116 patients
Amyloid precursor protein of thromboembolic disease	116 patients
Contraceptives	30 patients
Pregnancy	10 patients
Splenic diseases	35 patients

The source environment of the patients included in the study group was: urban 67%, rural respectively 33% with no statistical relevance (fig. 2)

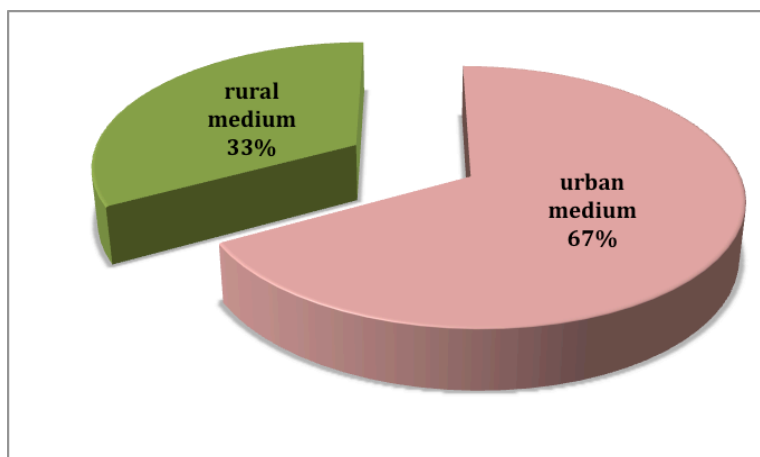


Figure 2
Medium of the patients submitted to analysis

The average age of the patients in the group study was $58.9 \text{ years} \pm 2.3 \text{ years}$.

The body mass index (BMI) was calculated for each patient, using the data from the observation sheets regarding the weight and height of the patients. The average BMI was $32.1 (\pm 2.05)$.

Patients' general characteristics such as age or weight together with the associated diseases such as diabetes, high blood pressure, malignant conditions, increase the risk potential of DVT [4, 5, 6]. Such patients need thromboprophylactic medication with LMWH (Nandroparine[®], Enoxaparine[®], Dalteparine[®]).

The obesity was identified in 53% of the analyzed patients and correlates with other risk factors such as sedentariness, difficult and insufficient postop mobilisation, the precarious electrolyte and fluid balancing, the possibility of septic complications, which are more frequent in these patients. Regarding the obese patients, there are also difficulties of examination in observing the DVT incipient signs.

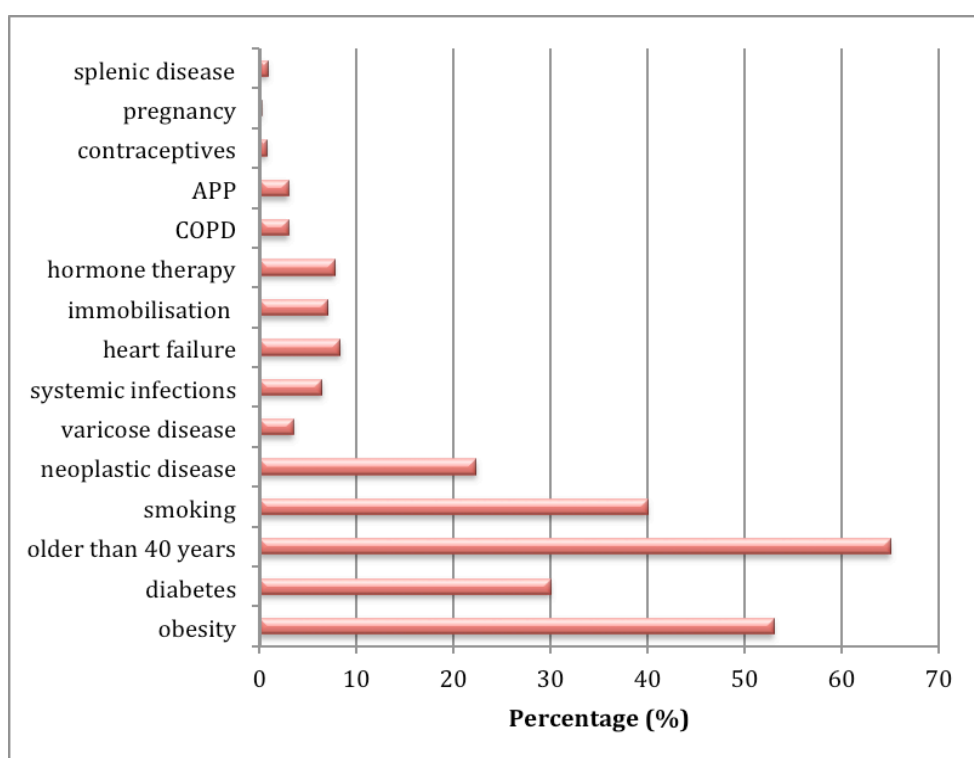


Figure 3

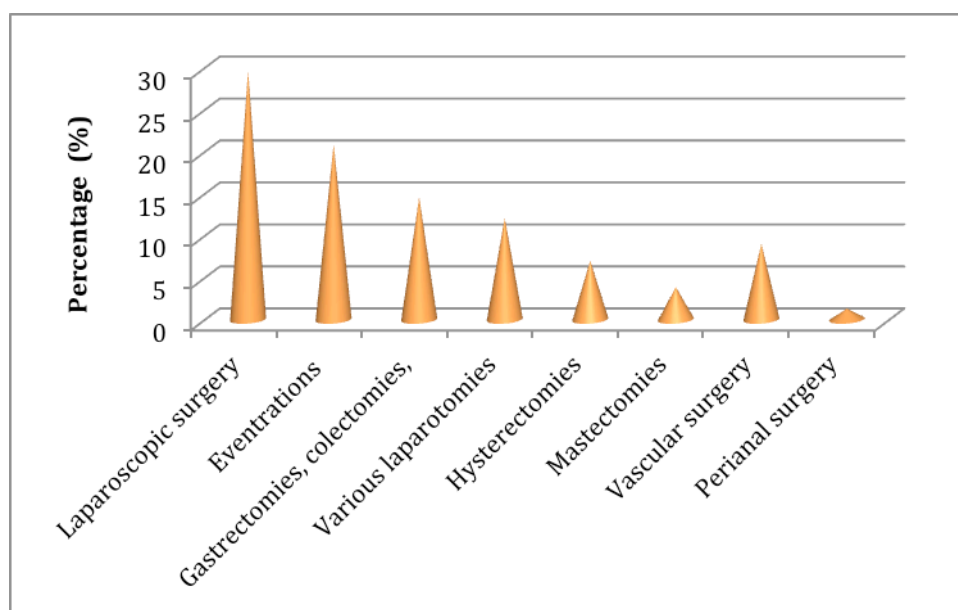
The incidence of DVT (deep venous thrombosis) risk factors in percentages

There is a series of risk factors that depend on the surgical procedure. For instance the laparoscopic surgeries (29.67%) develop specific additional risk factors which belong to the technique of the surgery: the created pneumoperitoneum induces modifications on the venous return at lower limbs level in relation with the pressure of CO₂ and the time of maintaining FLOWER position, and it also produces platelet aggregation and hypercoagulability (Table II and Figure 4).

Table II

The risk factors according to the type of surgery

Risk factors	no observations
Laparoscopic surgeries (gallbladder, appendix, hiatal hernias)	1150 cases
Eventrations	810 cases
Gastrectomies, colectomies, amputations of the rectum	565 cases
Laparotomies	470 cases
Hysterectomies	275 cases
Radical and modified mastectomies	150 cases
Vascular surgeries	350 cases
Perianal surgeries	50 cases
TOTAL	3820 cases

**Figure 4**

The incidence of risk factors according to the type of surgery

Perioperative prophylaxis of DVT is mandatory before the surgery for the patients included in the risk groups, because the incidence of DVT in patients having undergone an operation without heparin thromboprophylaxis rises between 10-40%. Approximately 25% of the thrombi situated in the proximity of the deep venous system of the lower limbs can determine pulmonary embolism.

In the absence of anticoagulation contraindications, heparinotherapy represents the election method for DVT prophylaxis in the majority of patients. DVT occurrence in anticoagulated patients in comparison with non-coagulated patients is 66% more reduced.

Neoplastic pathology, in our study, is correlated with a significantly high frequency of the risk of thromboembolic complications ($p < 0.01$), and therefore it is in accordance with the data from the literature. Thus, malignant tumors represented 6.96% from the total of the patients hospitalized during that period. 21.67% from the patients participating in the study who needed a surgery and 44.44% of the patients, despite thromboprophylaxis with LMWH, developed complications of DVT/PTE type.

The differences are statistically significant ($p < 0.01$). Therefore we can conclude that neoplastic disease represents a cause of thromboprophylaxis inefficiency. In a study developed by Suzuki and collab. It was discovered that the incidence of the pulmonary embolism in patients that had undergone a surgery for a malignant lesion was 22%, in comparison with only 0.32% for a benign condition [8].

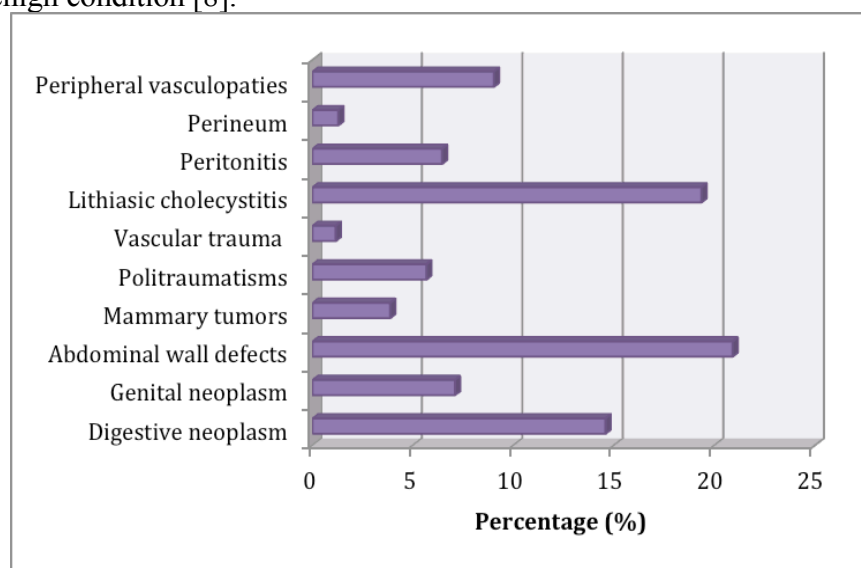


Figure 5

The incidence of thromboembolic risk factors in patients with additional diseases

On the other hand, clinical and biological monitoring of the anticoagulant therapy with LMWH is mandatory. Although it is considered to determine less complications than the undivided heparin, because it inhibits to a lesser extent the platelet function and does not increase the permeability at the microcirculation level, on the studied group there were registered 79 (2.04%) different types of hemorrhagic manifestations such as parietal abdominal hematoma, spontaneous or at wound level, externalized haemoperitoneum on the drain, axillary hematoma, upper gastrointestinal bleeding, macroscopic hematuria. Within the patients investigated, there were found only 2 cases of haemoperitoneum which a reintervention and blood transfusions were necessary, the other cases being solved conservatively.

Therefore DVT prophylaxis with LMWH proved to be safe and practically without major hemorrhagic or allergic complications, when the LMWH indication and therapeutic dosaged are well known and appropriately administered [9, 10, 11].

Table III

The risk factors for thromboembolism according to surgical disease intervention

Risk factors	No of observations
Neoplastic disease – digestive	565 cases
Neoplastic disease – genital	275 cases
Abdominal wall defects (primary and postop)	810 cases
Mammary tumors	150 cases
Politraumatisms	220 cases
Vascular trauma (iatrogenic accidents)	45 cases
Lithiasis Cholecystitis	750 cases
Peritonitis	250 cases
Perineum	50 cases
Peripheral vasculopathies	350 cases
TOTAL	3465 cases

As for the evaluation of the efficiency of preoperative thromboprophylaxis with LMWH by the incidence of DVT of lower limbs confirmed by Doppler ultrasound and its embolic consequences, we found 36 (0.92%) cases, of which 3 deaths. Nevertheless, the results of the study fit to the data provided by most of the publications regarding the positive appreciation of thromboprophylaxis. If it is taken into consideration that in the absence of heparinotherapy the incidence of DVT is between 15-40%,

we can say that the use of LMWH is efficient in controlling this postop accidents.

Our study complies with the literature data [4] and states that even if thromboprophylaxis with LMWH does not completely eliminate the risk of DVT/PTE occurrence, it remains the only pharmacologic and clinical method for the reduction of its incidence, of massive pulmonary thromboembolism, mortality and morbidity by PTE.

Conclusions

DVT of lower limbs with possible serious consequences (pulmonary thromboembolism which may lead to death) represents negative clinical events which often influence morbidity and mortality of the surgical interventions, especially in the field of general surgery, traumatology, orthopedy, gynecology, urology.

In association with cancer, numerous other factors involved in the occurrence of hypercoagulable state can predispose the patient to the developpement of thromboembolic events: age, obesity, diabetes, congestive heart failure, acute infections, smoking, contraceptives, as well as a series of events linked to the surgical act extended duration of the intervention, perioperative bleeding, node dissection in retroperitoneal space, perioperative transfusions, tissue dissection and postop prolonged immobilisation. 40% of the pulmonary embolism occurred in patients with a BMI >24. In this context it is considered to be sufficient arguments for the recommendation of the routine prophylaxis for the patients that are about to undergo surgery, when there is at least one risk factor.

Thromboprophylaxis with LMWH represents a safe treatment method, the postop hemorrhagic complications being minor, benefits outweighing the risks. In our study there was a rate of hemorrhagic complications of 2.04%, the majority being treated conservatively (97.5% of them). Only 2 cases of haemoperitoneum needed surgery, which represent only 0.5% in a thousand patients treated with LMWH. On the other hand the rate of thrombotic complications decreased under 1% (0.92%) and death by PTE was registered only in 3 patients (0.077%). Of all the patients that underwent thromboprophylaxis with LMWH and who still developed thromboses (inefficient thromboprophylaxis), 44.44% were patients with neoplasm, association statistically significant ($p < 0.01$). Thus, neoplastic disease is an important factor for the inefficiency of thormboprophylaxis with LMWH.

Because in surgery thromboembolic events represent important sources of postop morbidity and mortality, each patient that undergo surgery must be evaluated from the risk factors point of view, that can be responsible of the developpement of a thromboembolic event. Accordingly to this, the prophylactic strategy with LMWH should be established, but even so, the protection against the possible thromboembolic complications is not absolute.

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