Two models of thromboprophylaxis in acutely ill medical inpatients

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Abstract: Introduction. The risk of venous thromboembolism is equally high in medical patients admitted to the hospital and those treated in the surgery wards. Elderly people, who are immobilized due to heart failure, severe respiratory disease, ischemic stroke and cancer, represent patients at high risk of venous thrombosis. Current recommendations concerning antithrombotic prophylaxis do not specify the duration of prophylaxis in patients treated in the internal wards. **Objectives.** The objective of this study was to evaluate the efficacy and safety of two models of thromboprophylaxis with nadroparin in medical inpatients hospitalized for acute illnesses. **Patients and methods.** A total of 300 consecutive medical patients (155 M, 145 F, mean age, 67.8 ±4 years) were randomly assigned in an open-label study to two groups (1:1). Patients received thromboprophylaxis with nadroparin *s.c.* only during bed immobilization (the first group) or for 10 additional days (the second group). The follow-up lasted for three months after the end of thromboprophylaxis. Proximal deep veins thrombosis of lower limbs and death were considered as endpoints. Adverse effects of thromboprophylaxis were assessed, especially major bleedings and thrombocytopenia. **Results.** Both groups did not differ with regard to demographic characteristics or thrombotic risk factors. During a further 3-month follow-up of all the 300 patients, death of unknown causes or deep-vein thrombosis were found in 17 (5.6%) patients, including 2 patients who suddenly died. No such events were observed during the thromboprophylaxis period. In medical patients receiving thromboprophylaxis for a longer period of time than the immobilization there was a tendency to lower occurrence of death and deep-vein thrombosis within the first months following hospitalization (12 *vs* 5; p = 0.08). There were no major bleedings or thrombocytopenia in both groups during thromboprophylaxis and the subsequent follow-up. **Conclusions.** The study confirmed the effectiveness and safety of thromboprophylaxis with nadroparin in acutely ill medical inpatients, suggesting additional benefits from prolonged use of low-molecular-weight heparins observed during the first months after hospitalization.

Key words: efficacy, nadroparin, prophylaxis, safety, venous thromboembolism

INTRODUCTION

The risk for thromboembolism in medical inpatients is parallel to the risk observed in post-operative inpatients [1-3]. The most important study which results induced a change in thromboprophylaxis recommendations for medical inpatients was a multi-center study, the MEDENOX (MEDical patients with ENOXaparin) with randomization to enoxaparin and placebo [4]. Its results proved the efficacy of thromboprophylaxis in acute medical patients. The study proved that the daily dose of 40 mg of enoxaparin significantly reduces the risk for venous thromboembolism in such patients. The efficacy of thromboprophylaxis in medical patients was also the topic of a collective analysis by Cohen [5], in which it has been found that fondaparinux in venous thromboprophylaxis is effective in elderly, acute medical inpatients. Elderly patients were at a higher risk for venous thromboembolism due to a higher frequency of such disorders as: heart failure, severe respiratory disease, ischemic stroke and cancer in this population [6,7].

Venous thromboembolism is a major problem of public health. Its frequent asymptomatic course can be a common reason for death that could be omitted through prophylactic treatment [8]. It is however too rarely implemented due to its underestimation and the fear of hemorrhagic complications related to anticoagulant therapy [9,10]. The modernization of the diagnosis and therapy of venous diseases in the recent

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years has improved the treatment efficacy, and significantly contributed to the popularization of thromboprophylaxis [11]. The current Polish guidelines do not specify the duration of thromboprophylaxis in medical inpatients [12].

The efficacy and cost-effectiveness of venous thromboprophylaxis has been first demonstrated in post-operative inpatients and has already been administered, especially in surgical and orthopedic wards, for many years [13,14]. The significance of venous thromboprophylaxis in medical inpatients has been shown recently also in the Dentali et al. analysis [15], which presented the results of 9 randomized studies. The authors of the article emphasized the good results of prophylactic treatment, and stressed the necessity for further exploration of the risk for secondary thromboembolism after completion of prophylactic treatment.

The aim of the study was to assess the efficacy and safety of 2 models of thromboprophylaxis with low-molecular-weight heparin in medical patients.

PATIENTS AND METHODS

A group of 300 patients over 40 years of age, hospitalized for a medical disorder in the hospital in Rabka-Zdrój (tab. 1), in whom the expected duration of immobilization was at least 3 days, was enrolled in the randomized open label study.

In 2 years, 300 patients including 145 females (48.4%) and 155 males (51.6%) were enrolled. The majority of patients were over 70 years of age (62.7%) (tab. 2). The mean female age was 64.3 (±3.5), and male 69.2 (±4.5) years of age.

The identification of the thromboembolism risk factors was based on the following sources: the MEDENOX [4], the PROTECT study (PROphylaxis of Thromboembolic Events by Cetroparin Trial) [16], Cohen's collective analysis [5] and current antithrombotic prophylaxis, and venous thrombosis, treatment guidelines [12]. The most frequent thromboembolism risk factors in the presented study were: the age over 70 and heart failure (table 3).

The following inclusion criteria were adopted:

1) hospitalization period of at least 6 days
2) immobilization period of 3-14 days (an immobilized patient was defined as one who due to his disorder is unable to independently take a few steps
3) the age over 40
4) the absence of clinical (lower leg or lower extremity edema, lower extremity pain) or ultrasound (positive ultrasound compression test result) symptoms of lower extremity deep vein thrombosis.

The exclusion criteria were:

1) the necessity for nadroparin therapeutic dose administration
2) an immobilizing disease in the past 6 months
3) currently ongoing anticoagulant therapy (apart from acetylsalicylic acid, which is of no significance in thromboprophylaxis)
4) contraindications to low molecular weight heparin (hemorrhage high risk or previously found allergy to this medication)
5) cancer
6) mental disorders
7) alcoholism.

Cancer patients where excluded mainly due to being followed up in specialist centers which made permanent control impossible. The number of studied population being limited, the completeness of observation played a major role for the power of analysis.

The design of the study underwent a positive Bioethical Committee assessment of the Regional Medical Chamber in Kraków (nr 61/KBL/OL/2004). Each patient gave his informed consent to take part in the study.

The study was conducted it 2 stages: stage 1. – from the day of admittance until the completion of prophylactic with nadroparin, stage 2. – 90 days from the completion of prophylactic with nadroparin.

In stage 1 the patients where randomized in one of the two groups (I, II) 1:1. Nadroparin (Fraxiparine GlaxoSmithKline) prophylactic treatment was administered. Patients received the prophylactic dose of the medication following the manufacturer's instructions, according to their body mass: patients under 70 kg received 0.4 ml of nadroparine daily (that is 3800 I.U.), patients over 70 kg – 0.6 ml of nadroparine daily (that is 5700 I.U.). The dosage was chosen according to the Fraisse et al. study [17], which explored thromboprophylaxis in patients with chronic obstructive pulmonary disease exacerbation.

In group I nadroparin prophylactic treatment was administered only during patient immobilization, in group II during immobilization and for following 10 days.

During nadroparin administration patients were observed for any possible complications due to its administration, as bleeding or allergic reactions. During hospitalization the complete blood count with platelet count was calculated at least twice (at 3–5 days intervals), for possible thrombocytopenia. Hemorrhagic ecchymoses in medication injection areas were not considered a complication due to their very frequent occurrence in patients receiving heparin.

For confirmation or exclusion of deep vein thrombosis an ultrasound compression test in four points (with the use of the GE LOGIQ 200 PRO machine, and a 6–9 MHz linear probe) was performed three times in each patient: on the day of admision, upon completion of prophylactic treatment, and upon completion of a 3-month follow-up.

During stage 2 of the study patients were assessed for any potential venous thromboembolism symptoms. Upon discharge each patient received printed information about such venous thromboembolism symptoms as:

1) lower extremity edema
2) pain or erythema of a lower extremity
3) syncope
4) sudden heart throbbing sensation

Table 1. Reasons for immobilization of studied patients (n = 300)

Reason for immobilization	Number of patients	%
severe respiratory disease	165	55.0
heart failure (NYHA III/IV)	73	24.3
ischemic stroke	37	12.3
dehydration	23	7.7
acute lumbar pain	2	0.7

NYHA – New York Heart Association

Table 2. Age of patients (n = 300)

Age (years)	Number of patients	%
41–50	14	4.6
51–60	27	9.0
61–70	71	23.7
71–80	135	45.0
>80	53	17.7

5) sudden dyspnea or chest pain
6) sudden unexplained arterial blood pressure drop.

In the event of occurrence of any of the above mentioned symptoms, the patient was to immediately present at the hospital or to call the physician conducting the study. Patients, who had no alarming symptoms in observation, underwent an assessment in 90 (±10) days.

Patients' data was collected by means of a questionnaire based on patients' history and the performed examination. Such information as: age, sex, the reason for and duration of immobilization, the duration of nadroparin administration, the thromboembolism risk factors, the risk for thromboembolism, the ultrasound compression test results and venous thromboembolism symptoms found, as well as anticoagulant treatment complication symptoms, was included in the questionnaire.

The safety of implemented prophylactic treatment was assessed by the frequency of bleeding incidents, trombocytopenia and local skin reactions. The bleeding was recognized as the end point if overt and requiring transfusion of at least 2 units of packed red cells, or correlating with a fall in hemoglobin concentration of 2.0 g/dl. A drop in the trombocyte count of 50% compared to initial value was regarded as trombocytopenia. A rash at the injection site was recognized as a local skin reaction.

Lower extremity deep-vein thrombosis confirmed by a four point ultrasound compression test, upon completion of prophylactic treatment or during a 3-month follow-up, or death regardless of its reason, were considered end points. Adverse effects of nadroparin, especially hemorrhagic complications were assessed.

Table 3. Venous thromboembolism risk factors in studied patients (n = 300)

Risk factors	Number of patients	%
age >70 lat	188	62.7
heart failure	154	51.3
cigarette smoking	30	10.0
obesity	27	9.0
lower extremity varices	17	5.6
dehydration	8	2.6
polycythemia	7	2.3
past venous thrombosis	3	1.0

Statistical analysis

A statistical analysis was performed with the use of the STATISTICA 7.1 PL package. The number of patients was assessed from the incidence of thromoboembolic incidents in to-date studies, accepting standard values of assumed errors type I and II. The collected data was then summarized and descriptive statistics - statistical mean, and standard deviation (SD) were derived. For qualitative variables, the number and percentage of patients in each group were obtained. Shapiro and Wilk test was employed to check if the data distribution was normal. The comparison of the two groups was done with the use of the Student's t test and if the data distribution was different from normal with the Mann and Whithney test. The correlation analysis was performed for the assessment of relations between variables. In all analyses, the results for which test probability value p was lower than the assumed relevance level ($p < 0.05$), were considered significant.

RESULTS

Initial characteristics

Both groups, 150 patients each, did not differ significantly either in age (mean age: group I – 66.2 y., group II – 69.4 y.; $p = 0.9$), or sex (M: group I – 54.0%, group II – 49.3%; $p = 0.4$). The reasons for immobilization of studied patients are given in table 1. The immobilization duration was 37 days (mean 4.8 days; in group I – 5.1 days, and in group II – 4.5 days). Among risk factors a statistically important difference in both groups (I:II) concerned cigarette smoking (14%:6%, $p = 0.02$) and dehydration (4.67%:0.67%, $p = 0.03$). The average number of risk factors in group I was 1.43, and in group II – 1.44 (tab. 4).

The course of thromboprophylaxis

The mean duration of nadroparin thromboprophylaxis in group I was 5.1 days, in group II 14.5 days ($p = 0.03$). During prophylactic treatment no patient dropped out of the study

Table 4. Venous thrombosis risk factors in patients in both randomized groups

Risk factors	Group I (n = 150)	%	Group II (n = 150)	%
age >70 years	93	62.0	95	63.3
heart failure	72	48.0	82	54.7
cigarette smoking	21	14.0	9	6.0
obesity	14	9.3	13	8.7
lower extremity varices	6	4.0	11	7.3
dehydration	7	4.7	1	0.7
polycythemia	3	2.0	4	2.7
past venous thrombosis	2	1.3	1	0.7
mean	1.43	–	1.44	–

nor any death occurred. The complete blood count performed at this time in most patients was within the normal value range, as were the results of other standard laboratory tests. No heparin induced thrombocytopenia was found. Hemorrhagic ecchymoses occurred in injection sites in all patients, however no important hemorrhagic complications were found. An itching, micropapular rash at the nadroparin injection site, occurred as an allergic reaction in the last (6.) day of its administration, in one patient. The rash was gone after the administration of 1% hydrocortisone. Upon the day of completion of thromboprophylaxis the ultrasound compression test was negative in all patients.

The follow-up of patients after completion of thromboprophylaxis

During the follow-up of 3 months' duration the end points occurred in 17 (5.6%) of all 300 patients. This group did not differ from the other patients regarding demographics and the reason for hospitalization. Two sudden deaths were observed in day 30 and 52 after completion of prophylactic treatment (its reasons not being verified at autopsy), and 15 (5%) cases of documented proximal lower extremity deep vein thrombosis (positive result of ultrasound compression test). End points in the group of shorter prophylactic treatment period occurred in 8% (12 persons), and in 3.3% (5 persons) in the long duration prophylactic treatment group. There were (1.3% – 2 persons) deaths observed in the shorter duration prophylactic treatment group. Of 17 patients with demonstrated end points, the prophylactic treatment time matched the immobilization time in 12, and in 5 patients it lasted 10 days longer.

Proximal deep vein thromboembolism

The mean patient age with ultrasound proximal deep vein thrombosis symptoms was 71 years. The females constituted 52.9% (n = 9) of the population. In 10 patients (66.6%) the period of nadroparin administration equaled the immobilization time (group I), in the remaining 5 patients it lasted 10 days longer (group II). Patients in whom deep vein thrombosis occurred despite the extended period of prophylactic treatment were in the high venous thromboembolism risk group. The mean number of risk factors in this group was 3.4 (mainly elderly age, heart insufficiency, obesity and cigarette smoking). In the group of short duration prophylactic treatment the mean was lower and equaled 2.3. In individuals with a positive end point (n = 17) the most frequent reason for immobilization was a severe respiratory disease (52.9%). The immobilization time in the confirmed deep vein thromboembolism group (n = 15) was 8 days on the average and was nearly twice as long as the mean immobilization time in the rest of the patients. The most frequent venous thromboembolism risk factor was heart insufficiency found in 13 patients (86.6%).

DISCUSSION

Due to the confirmed high risk of venous thromboembolism in medical patients, guidelines assessing the risk factors for venous thromboembolism and concerning prophylactic treatment of this disease in medical inpatients [18,19], were developed. The mentioned study correlates with the ongoing discussion on the optimization of prophylactic treatment in medical inpatients and the protocol of the ongoing EXCLAIM [20] study (EXtended CLinical prophylactic treatment in Acutely Ill Medical patients) indicates the prevalence of opinion about benefits related to prophylactic treatment period extension. As with age the risk for venous thromboembolism and its complications rises [21], only patients over 40 took part in the mentioned study. Similarly, patients over 40 were enrolled in the MEDENOX study [4]. In the PROTECT study [16] the range of patient age was 18–85 years, and the Cohen et al. collective analysis [5] enrolled patients over 60 (tab. 5). Elderly age is an important venous thromboelmbolism risk factor [22,23].

Such diseases as severe respiratory disease, heart failure and sciatica, based on the example of the MEDENOX [4] study and on the PROTECT [16] study (cerebrovascular disorders with hemiparesis) were included a. the study exclusion criteria.

Nadroparin, a low molecular weight heparin was used in the study. In large multi-center studies concerning venous thromboprophylaxis other low-molecular-weight heparins were used more often (e.g. enoxaparine [4], certoparine [16], and standard heparin [24] as well as synthetic pentasaccharide fondaparinux [5]).

The measure of safety of administered prophylactic treatment is the ratio of patients with hemorrhages. A comparison of the presented study and more significant studies with regard to efficacy and safety of thromboprophylaxis revealed similarities in efficacy and an unexpected absence of serious

Table 5. The comparison of the presented study results in comparison with selected multi-center studies

	MEDENOX study	Cohen collective analysis.	PROTECT study	Presented study
reason for hospitalization	heart failure, respiratory failure, acute infection, inflammatory bowel disease	heart failure, respiratory insufficiency, acute infection	stroke	heart failure, severe respiratory disease, stroke, dehydration.
number	291	321	272	300
age	>40 years	>60 years	18–85 years	>40 years
introduced medication	enoksaparin 40 mg/d	fondaparinux 2.5 mg/d	certoparin 3000U anty-Xa	nadroparin 0.4–0.6 ml/d
main diagnostic procedures	venography, Doppler ultrasound	venography	computed tomography, Doppler ultrasound	ultrasound compression test
immobilization time	at least 6 days	at least 4 days	12–16 days	3–14 days

hemorrhages in the study group, the reason for it possibly being the inclusion and exclusion criteria which eliminated cancer patients (tab. 6).

The percentage of patients in whom venous thrombosis occurred despite the prophylactic treatment is comparable throughout all the quoted studies. In the presented study a 3800 - 5700 I.U. dose of nadroparin was used, and the percentage of venous thrombosis found in patients despite the administered prophylactic treatment was 5.8%. This result was very close to the one obtained in the Cohen [5] collective analysis in which the administration of a 2.5 mg fondaparinux prophylactic treatment correlated with documented venous thrombosis in 5.6% of patients.

The discussed study included also cerebral ischemic stroke inpatients. These patients are at an especially high risk of venous thrombosis due to lower extremity paresis and, pulmonary embolism is often a cause of death [25,26] in these patients.

It has been estimated that the incidence of venous thromboembolism in these patients ranges from 30 to 75%, and mortality for pulmonary embolism is 1 – 2% [27]. The analysis of efficacy of thromboprophylaxis with certoparin and unfractionated heparin in ischemic cerebral stroke was presented in the PROTECT study [16]. It has been demonstrated that both types of used heparins are of equal efficacy. The symptoms of venous thromboembolism occurred in 7% of the certoparin patients group and in 9.7% of the standard heparin patients group. In the presented study patients with ischemic cerebral stroke were 12.3% (that is 37 individuals). In this group despite the introduced prophylactic treatment the symptoms of the venous thromboembolism occurred in 3 patients (8.1%).

Studies concerning thromboprophylaxis in medical patients conducted in various centers differ slightly regarding indications for thromboprophylaxis, patients' age, the risk factors, implemented diagnostic procedures, duration of prophylactic treatment and duration of immobilization.

The type of medication used is also the differentiating factor (tab. 5). The study results clearly indicate however, that such a population of patients gains measurable profits from thromboprophylaxis .In contrast to the discussed study in the publications mentioned in this discussion patients were not randomized in groups of various duration of prophylactic treatment because the relation between prophylactic treatment efficacy and its duration was not assessed. The safety of used prophylactic treatment was not related to its duration and the patient immobilization duration. This study demonstrated that clear clinical benefits can be derived from prophylactic treatment in a small hospital, in a diverse group of medical patients. The weakness of the study was that despite the initial assumption its strength did not allow the authors to find statistically significant differences between groups of various prophylaxis time, what is at least partially related to an unexpected absence of important hemorrhagic complications. The inclusion criterion that is, the exclusion of cancer patients and their scrupulous medical supervision contributed most probably to this observation. Apart from that, the ultrasound machine without the

Table 6. Safety and efficacy of thromboprophylaxis in selected studies

Study	Percentage of patients with		
	venous thrombosis	death	hemorrhage
MEDENOX (n = 360)	5.5	0.7	3.4
Cohen et al. (n = 321)	5.6	3.3	0.2
PROTECT (n = 272)	7.0	2.6	1.1
Bergman and Neuhart (n = 207)	4.8	1.7	0.5
presented study (n = 300)	5.8	0.6	0

colour Doppler function could not have detected all the cases of venous thromboembolism, but was sufficient for the assessment of ultrasound compression test results, a recommended screening exam in such a clinical setting.

In summary, the discussed study confirmed the safety and efficacy of thromboprophylaxis with nadroparine in acute medical patients. A tendency for a rarer occurrence of end points in patients receiving low molecular weight heparin, for longer than only during immobilization, was observed. This suggests that patient mobilization related to an overall patient improvement does not fully eliminate the risk for venous thromboembolism in this group of patients. There is a need for larger medical inpatients studies in order to assess if prophylactic treatment prolongation beyond the immobilization time will result in larger clinical benefits than prophylaxis limited to the immobilization time.

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