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Venous thromboembolism prophylaxis in hospitalized patients with pneumonia: a prospective survey

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Summary. *Background:* Guidelines for prevention of venous thromboembolism recognize pneumonia and changes in respiratory status as risk factors. There is little information on the preventive use of low-molecular-weight heparin (LMWH) in hospitalized patients with pneumonia.

Methods: We prospectively screened 1067 admissions to our hospital for preventive use of LMWH according to the American College of Chest Physicians (ACCP) guidelines. The analysis included 168 patients with pneumonia (age 74 ± 16 years, 56% men). The primary and secondary outcomes were treatment with LMWH in eligible patients and LMWH use according to guidelines (daily dose, duration of treatment).

Results: LMWH use was indicated in 126 (75%) patients and 119 (94%) were actually treated. In 41% of patients treatment was according to the ACCP guidelines. The dose and duration of LMWH treatment were appropriate in 61% and 66% of patients, respectively. Non-use of LMWHs was not associated with clinical and demographic characteristics. Adverse effects included bleeding (N = 7) and thrombocytopenia (N = 2) but were not associated with fatality. Prolonged treatment with LMWH was associated with adverse effects ($P < 0.05$).

Conclusions: Implementation of LMWH prophylaxis for venous thromboembolism in hospitalized patients with pneumonia reached 94%. Adherence to ACCP guidelines was complete in 41% of patients. Prolonged treatment with LMWH was associated with non-fatal adverse effects, which calls for timely withdrawal of LMWH once no longer indicated.

Key words: Bleeding, low-molecular-weight heparin, pneumonia, thromboprophylaxis, venous thromboembolism.

Introduction

Venous thromboembolism (VTE) is a common complication in many chronic diseases [1]. Several predictors of VTE have been identified in hospitalized patients [2], which has led to the development of risk scores for patient assessment and management decisions [3, 4]. In general, age, limited mobility from any cause, chronic disease, inflammation and respiratory failure contribute most to increased risk [2].

Most reports have focused on elderly surgical patients or patients with chronic non-inflammatory disease, who are likely to reach the threshold for use of low-molecular-weight heparin (LMWH) [4, 5], but less is known about LMWH use in hospitalized patients with pneumonia or pulmonary disease [6, 7]. Although many patients with pneumonia are younger, with less pronounced respiratory insufficiency and less chronic disease than other patients seen in hospitals, many of them may be eligible for treatment with LMWH. Whether guidelines are implemented as appropriate in hospitalized patients with specific underlying diseases is insufficiently investigated. It is also unknown whether patient characteristics or other determinants may cause reluctance to use LMWH.

In our prospective survey we aimed to investigate the implementation of VTE prevention and LMWH prophylaxis guidelines in hospitalized patients with pneumonia. We also followed any LMWH-associated adverse effects and sought to identify predictors of LMWH non-use or inappropriate use.

Methods

Study design

We conducted a prospective observational survey at the University Clinic of Respiratory and Allergic Diseases in Slovenia. All admissions to our tertiary-care hospital (total 163 beds) during a two-month period in January–March 2008 were screened for VTE prophylaxis with LMWH. The analysis focused on patients with pneumonia during index hospitalization. Patients were excluded if they were under 18 years of age, were taking part in another study, had to be isolated because of disease or if their hospital stay was ≤2 days. The Slovenian National Ethics Committee approved the study protocol. Patients were treated according to good clinical practice guidelines and the survey did not affect their treatment or care.

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Data collection

A standard screening form was developed for data collection, assessment of indication for VTE prophylaxis and LMWH treatment. All admissions were initially screened by an investigator (PJ) and a clinician (ML). During a testing period of two weeks, no major differences in enrolment decisions were observed. For the rest of the study period, the investigator continued with screening and enrolment and the clinician was consulted in borderline or unclear cases. Finally, both investigators revised all the enrolled patients for inclusion criteria and quality of the collected data. At admission, we collected data on patients' demographics, medical history, risk factors for VTE, indications and contraindications for treatment with LMWH and laboratory parameters (serum creatinine, platelet count, hemoglobin level, international normalized ratio [INR]). Patients with indication for VTE prophylaxis and those who were treated with LMWH were followed throughout their hospital stay. We also followed the LMWH daily dose and duration of treatment, as well as any adverse effects such as bleeding or thrombocytopenia. In all patients, we checked whether the decision for VTE prophylaxis was based on a specifically developed clinical pathway [8].

VTE prophylaxis

VTE prophylaxis was assessed according to American College of Chest Physicians (ACCP) guidelines [4]. The main criteria were (i) active cancer or specific cancer therapy; (ii) immobilization; (iii) congestive heart failure; (iv) acute respiratory disease; (v) severe infections; (vi) history of VTE; or (vii) additional risk factors for VTE. Limited mobility was defined as being confined to bed most of the time or as a patient's inability to walk for more than 15 m. Indications for treatment with LMWH were identified from the admission history, physical examination, disease-progress notes and hospital discharge letters. Relative or absolute contraindications for LMWH therapy were: active bleeding, known hypersensitivity to LMWHs, uncontrolled hypertension, glomerular filtration rate (GFR) <30 ml/min (calculated using the MDRD equation [9]), history of heparin-induced thrombocytopenia and active gastroduodenal ulcer. Daily dose and treatment duration were considered appropriate when in compliance with definitions in the ACCP guidelines [4]. Since no clear guidance for duration is given, treatment was considered to be appropriate until indications for VTE prophylaxis were met. Dalteparin (5000 IU once daily or 2500 IU once daily if greater risk of bleeding present), enoxaparin (4000 IU once daily) or nadroparin (5700 IU in patients >70 kg, 3800 IU in patients ≤70 kg once daily) were considered appropriate for VTE prophylaxis.

Statistical analysis

Descriptive statistics were used to characterize the patients. Continuous variables are presented as median value and interquartile range (IQR). Categorical variables are presented as absolute numbers and percentages. To evaluate differences between groups of patients with and without pneumonia, and between LMWH-eligible patients according to actual LMWH treatment, Student's *t*-test, the chi-squared test and the Mann–Whitney U test were used as appropriate. Uni- and multivariate logistic regression analysis were used to investigate the

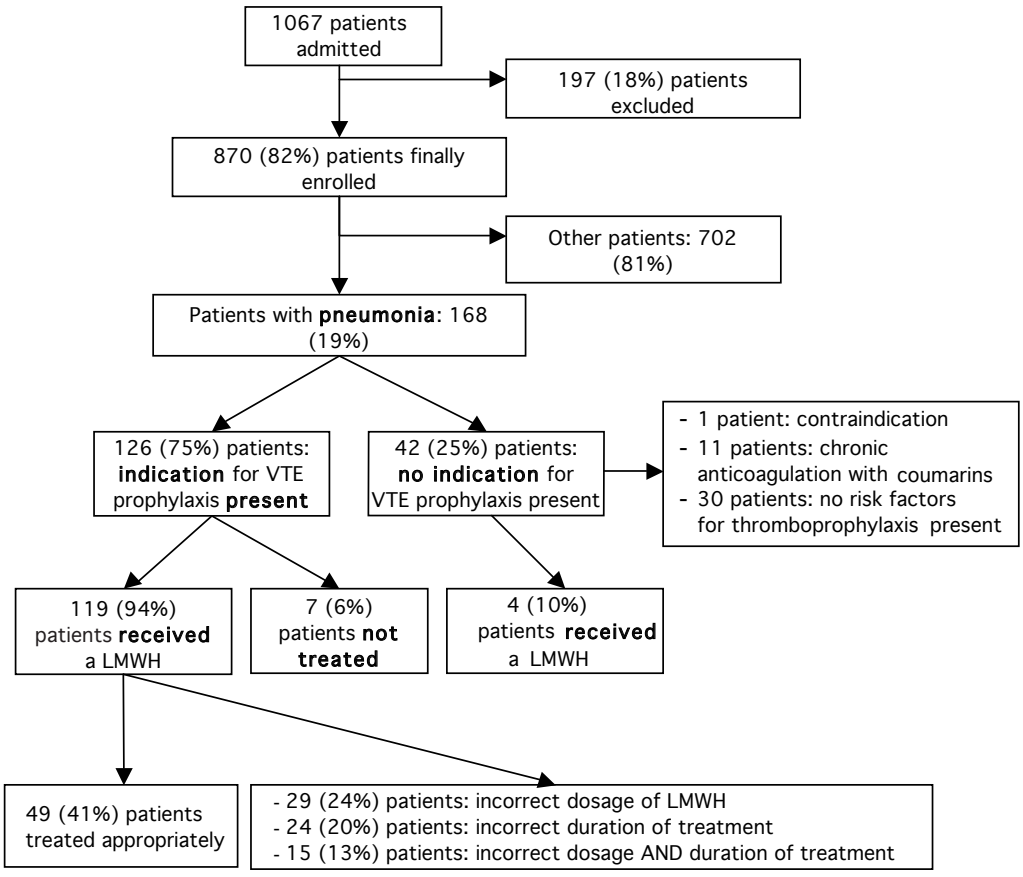

Fig. 1. Study flowchart

association between LMWH use and patient characteristics. The same methods were used to identify predictors of adverse effects. We report odds ratios and corresponding 95% confidence intervals. SPSS 12.0 software was used for all calculations. For all tests a P value ≤0.05 (two-sided) was considered statistically significant.

Results

During a period of two months we screened 1067 patients and, after exclusion of 187 patients on the basis of predefined criteria, the final sample comprised 870 patients (median age 72 (60, 79); 55% men). Pneumonia was diagnosed in 168 (16%) patients (median age 74 (62, 81); 56% men) (Fig. 1). In total, 25 patients died during their hospital stay (all had indications for VTE prophylaxis). There was no difference in the death rate in patients who received LMWH and those who did not (19% vs. 29%, P = 0.55). VTE prophylaxis with LMWH was indicated in 126 (75%) patients with pneumonia and 119 (94%) actually received LMWH. When compared with patients without indication for VTE prophylaxis, they had more co-morbidity, were older and had a longer hospital stay (Table 1). Next to limited mobility, 75% of patients had at least one additional major risk factor for VTE prophylaxis. Acute respiratory insufficiency was present in 57%, and 48% of patients were over 75 years of age (Table 1). Nadroparin (55%) or dalteparin (42%) were used in most patients, whereas very few patients received enoxaparin (3%). The clinical pathway was completed for 13 (11%) patients who received LMWH. The VTE prophylaxis was effective, as no clinically evident thrombotic events were recorded throughout the study.

In uni- and multivariable analysis, non-use of LMWH prophylaxis in eligible patients was not associated with clinical and demographic characteristics (P >0.2 for all). Patients eligible for VTE prophylaxis were hospitalized for a total of 1406 days and LMWH use was indicated during 1142 days. The actual duration of treatment in this group of patients was 1096 days and LMWH treatment was appropriate for 761 days. There was no significant difference between duration of indication for VTE prophylaxis and actual duration of LMWH treatment (9.2 ± 6.4 days vs. 9.2 ± 6.1 days, P = 0.94). Dose and duration were appropriate in 61% and 66% of patients, respectively, but only 49 (41%) patients were treated according to the ACCP guidelines during the period of indicated VTE prophylaxis (Fig. 2).

Table 1. Patient characteristics and risk factors for venous thromboembolism. Data are presented as median (interquartile range) or number (proportion)

	All patients	LMWH indicated	LMWH not indicated	*P*
Number	168	126	42	NA
Age [years]	73 (62–81)	73 (66–82)	61 (50-75)	<0.001
Men	94 (56%)	70 (56%)	24 (57%)	0.86
Length of stay [days]	9 (7–13)	9 (7–14)	8 (6–11)	0.02
Heart rate [beats/min]	96 (81–110)	98 (82–113)	90 (76–103)	0.02
Systolic blood pressure [mmHg]	147 (118–150)	135 (115–145)	141 (130–156))	0.01
Diastolic blood pressure [mmHg]	70 (70–87)	80 (70–85)	84 (79–90)	0.06
Serum creatinine [mmol/l]	92 (61-99)	76 (62–99)	74 (57–92)	0.64
Estimated glomerular filtration rate [ml/min]	81 (59–107)	76 (59–102)	94 (63–114)	0.34
Hemoglobin [g/l]	117 (116–140)	128 (116–139)	132 (117–143)	0.73
Platelet count [x10^9]	205 (203–359)	270 (194–357)	311 (242–423)	0.03
Diabetes mellitus	31 (18%)	24 (19%)	7 (17%)	0.73
Limited mobility	129 (77%)	126 (100%)	3 (7%)	<0.001
Major risk factors				
Acute heart failure	11 (6%)	11 (9%)	0	0.05
Acute respiratory failure	74 (44%)	72 (57%)	2 (5%)	<0.001
Cancer	27 (16%)	23 (18%)	4 (9%)	0.18
Infection	168	126	42	<0.001
History of VTE	2 (1%)	2 (2%)	0	0.41
Minor risk factors	68 (40%)	61 (48%)	7 (17%)	<0.001
Age ≥75 years				
Chronic heart failure	18 (11%)	16 (13%)	2 (5%)	0.15
Chronic respiratory failure	20 (12%)	20 (16%)	0	0.01
Hormonal therapy	3 (2%)	3 (2%)	0	0.31

VTE venous thromboembolism; *NA* not applicable.

Treatment had to be interrupted in nine (8%) patients because of adverse effects: seven cases of bleeding and two of thrombocytopenia. Although not contributing to fatal outcome, adverse effects were more common in patients who died (22% vs. 4%, $P = 0.13$). Adverse effects were associated with prolonged treatment (3 cases of bleeding, 2 cases of thrombocytopenia) and overdosing (2 cases of bleeding). Prolonged treatment with LMWH (per day increase: odds ratio [OR] 1.14, 95% confidence interval [CI] 1.04–1.25; treatment too long: OR 7.34, 95% CI 1.78–30.30) and cancer (OR 4.09, 95% CI 1.00–16.72) were associated with occurrence of side effects. In an age-adjusted model, prolonged treatment with LMWH (per day increase: OR 1.13, 95% CI 1.04–1.26; treatment too long: OR 23.39, 95% CI 3.67–149.22) remained the strongest risk predictor (Table 2).

Discussion

Our prospective study showed good implementation of VTE prophylaxis with LMWH in hospitalized patients with pneumonia. Although 94% of eligible patients received LMWH, the duration of treatment and the daily dose were in complete accordance with the guidelines in only 41% of patients. Treatment had to be interrupted in 8%, in association with LMWH use beyond the indicated timeframe. Adverse effects did not contribute to fatal outcome.

Indication for VTE prophylaxis was present in many patients (75%), possibly due to more severe infection, the presence of several risk factors (co-morbidity) or advanced age. Significant proportions of patients eligible for VTE prophylaxis have been reported in other studies that included pulmonary patients. For example, the IMPROVE study [10] and a recent study from the USA [11] reported an indication in 43% and 51% of patients, respectively. The ENDORSE study, however, reported that all patients with pulmonary infection met the criteria for VTE prophylaxis [12].

In our study an exceptionally high proportion of patients with indication for VTE prophylaxis actually received LMWH (94%). This is a higher proportion than in some other recent studies such as ENDORSE [12] and IMPROVE [10], where only 40% and 61% of unselected patients at risk received prophylaxis. Few studies have assessed patients with pulmonary disease. In a study by Amin et al. [7], 44% of patients had severe lung disease and 50% received VTE prophylaxis. In addition, a clinically important finding was that rates varied with

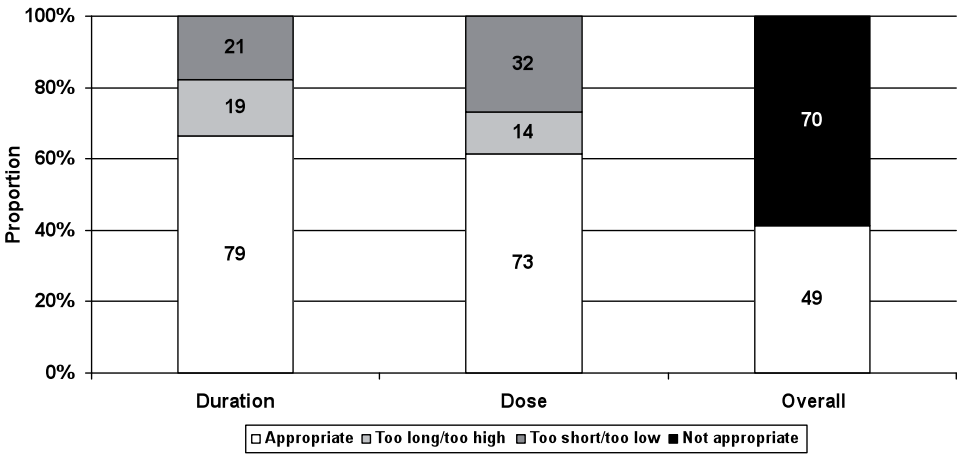

Fig. 2. Low-molecular-weight heparin treatment according to guidelines. Numbers represent number of patients

Table 2. Predictors of adverse effects. Numbers are odds ratio and 95% confidence intervals

	Univariate model	Multivariate model [LMWH treatment days]	Multivariate model [LMWH treatment too long]
LMWH treatment [per day increase]	1.14 (1.04–1.25)	1.13 (1.04–1.26)	NA
LMWH treatment [too long vs. appropriate]	7.34 (1.78–30.30)	NA	23.39 (3.67–149.22)
LMWH high dose	2.69 (0.49–14.88)	NA	NA
Age [per decade]	1.47 (0.82–2.64)	NA	NA
Men	2.49 (0.59–10.47)	NA	NA
Cancer	4.09 (1.00–16.72)	3.88 (0.80–18.93)	7.17 (1.25–41.05)
Estimated glomerular filtration rate [< 60 ml/min]	3.33 (0.87–13.25)	NA	NA

LMWH low-molecular-weight heparin; *NA* not applicable.

the specialty of the attending physician: internal medicine specialists and pulmonologists treated only 34% of their patients at risk. Another study in a tertiary-care center reported infectious disease in 57% of patients but only 31% received VTE prophylaxis [13], and in a retrospective chart review by Rahim et al., some form of prophylaxis was received by 49% of patients with pneumonia [6]. The reasons for the much higher rate of VTE prophylaxis with LMWH in our study are probably manifold. First, patients with infectious disease are known to be at high risk for VTE and are part of all major thromboprophylaxis studies [14–16]. ACCP guidelines [4] stress the importance of VTE prophylaxis in acute infection. Second, a previous analysis of LMWH use for VTE prophylaxis at our hospital resulted in development of a clinical pathway for treatment with LMWH [8]. Although our results showed a limited contribution of the clinical pathway, it is likely that awareness among physicians was increased. It is also possible that physicians implement good clinical practice beyond acute illness but do not perform the paperwork. Lastly, the study was set in a tertiary-care pulmonary hospital that admits the most severely ill patients, frequently of advanced age and with many co-morbidities or risk factors.

Although the absolute number of days with indication present and the absolute number of days of LMWH treatment did not differ significantly (1142 days vs. 1096 days), this has to be interpreted cautiously. Treatment was in complete agreement with the guidelines for 761 days but many patients were treated beyond indication, therefore it is very likely that over-treatment balanced non- or under-treatment in 7 and 21 patients, respectively. Clinically the most important message of this analysis is the proportion of patients treated with the correct dose (61%) for the correct period of time (66%), or both (41%). Previous studies focused primarily on the presence of VTE prophylaxis, whereas very few followed treatment implementation according to guidelines. In one such study, 31% of patients with severe lung disease received appropriate prophylaxis, defined by type of VTE prophylaxis, regimen, daily dosage and duration of therapy [7]. Stark et al. [17] defined an appropriate regimen of thromboprophylaxis only by its dosage, and reported that only 5% of patients were treated appropriately. As there is very little information on this specific topic, it remains unclear whether these proportions are satisfactory or not. In any case, our study showed high adherence to the guidelines and is comparable with the proportions in cardiovascular disease [18, 19].

VTE prophylaxis with LMWH is associated with adverse effects, predominantly bleeding and thrombocytopenia. Relatively high proportions were reported in the MEDENOX study (1% and 3%) and were attributed to enoxaparin [20]. In the PREVENT study, dalteparin was used and adverse effects occurred in 0.5% of patients [6]. An observational study by Peterman et al reported that only 0.1% of patients developed minor bleeding or thrombocytopenia [21]. The proportions in our study were much higher: bleeding 6% and thrombocytopenia 2%. This can in part be attributed to prolonged treatment with LMWH and to cancer. Other reasons remain unclear but could reflect better screening and detection of bleeding, unrecognized hypercoagulable conditions such as cancer or heart failure, and drug interaction. Indeed, regarding the polypharmacy in internal-medicine patients, considerable risk for interaction exists, particularly in patients with co-morbidity [22, 23]. In our study multivariate analysis was performed with limited number of events, which calls for replication in a larger sample size.

Our study has to be interpreted in light of some limitations. First, the decision for VTE prophylaxis was based on the information available from the medical records and brief contact with patients, thus the true need for VTE prophylaxis could have been underestimated. We relied on the available information and did not indicate additional examinations or tests as that would have interfered with the attending physician and could eventually have led to bias. Second, most of the work was performed by an investigator without much clinical experience. However, there was negligible decision discordance during an initial period of double-checking with a clinician, and supervision throughout the study ensured appropriate interpretation of the guidelines. Third, per study design, we did not follow patients without an indication for VTE prophylaxis on screening (N = 42). Nevertheless, considering the reduction in the number of risk factors for VTE prophylaxis between admission and discharge in patients receiving LMWH, we feel it is very unlikely that a significant proportion of the 42 patients in question would have reached the threshold for LMWH treatment post-admission. Fourth, because of the small sample size some findings have to be interpreted with caution, and predictors of adverse effects need to be reanalyzed in a larger sample. Lastly, the appropriate duration of treatment was defined as the period during which the patient met the criteria for VTE thromboprophylaxis. This definition can be argued, as the risk probably does not terminate abruptly (as should treatment when following this approach) but rather decreases gradually. The duration of thromboprophylaxis should therefore be addressed in a prospective study in a large sample, which was beyond the scope of this study.

In conclusion, this study found an exceptionally high rate of VTE prophylaxis with LMWH in hospitalized patients with pneumonia. Adherence to ACCP guidelines was less strict for dosage and particularly for duration of treatment. The latter was associated with non-fatal adverse effects, which calls for timely withdrawal of LMWH when no longer indicated. In clinical practice, the indication for VTE prophylaxis has to be re-examined once patients regain mobility and/or do not require oxygen support. It may be worthwhile to promote the use of a specifically developed clinical pathway, which was largely neglected in our study. By doing so, we could improve our adherence to guidelines and reduce the occurrence of side-effects resulting from unnecessarily prolonged treatment.

Conflict of Interest
The authors declare that there is no conflict of interest.

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