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Original Article

Frequency of renal impairment, advanced age, obesity and cancer in venous thromboembolism patients in clinical practice

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ABSTRACT

Introduction: Low molecular weight heparin (LMWH) dosed by weight is recommended as first-line therapy for the initial treatment of venous thromboembolism (VTE) and as monotherapy for long-term treatment of cancer-related VTE. In 'special populations' such as those with renal impairment or the elderly, weight-based dosing may be excessive, while capping the dose in obese patients may lead to inadequate dosing.

Objectives: We determined the prevalence of 'special population' characteristics (renal impairment, advanced age, obesity) and cancer among VTE patients in clinical practice, and assessed whether these characteristics appeared to influence the type and dose of anticoagulants prescribed.

Methods: During 2004-05, among consecutive patients with VTE at two large Canadian hospitals, the proportions with the above characteristics were calculated and treatments prescribed were determined.

Results: Of 524 VTE patients, 31% were >75 years. Moderate renal impairment (CrCl 30-59 cc/min) was present in 20% and severe renal impairment (CrCl <30 cc/min) in 5% of patients. LMWH was prescribed to 67% of patients with severe and 83% of patients with moderate renal impairment. Body weight was >100 kg in 15% of patients. Underdosing of LMWH by >10% was documented in 36% of such patients compared with 8% of patients < 100 kg ($p<0.001$). Among 26% of patients with active cancer, only 1/3 were prescribed LMWH monotherapy.

Conclusions: In clinical practice, renal impairment, advanced age, obesity and cancer are frequently present in patients with VTE. A considerable proportion of these patients may not receive the optimal type or dose of medication to treat VTE.

INTRODUCTION

Evidence-based guidelines for the treatment of venous thromboembolism recommend the use of low molecular weight heparin (LMWH), dosed by patient weight, over unfractionated heparin (UFH) as first-line therapy for the initial treatment of most patients with venous thromboembolism (VTE), followed subsequently by three or more months of oral vitamin K antagonists. For patients with cancer-related VTE, LMWH monotherapy (i.e. without subsequent warfarin) dosed by patient weight is strongly recommended as first line therapy (1).

Weight-based dosing of LMWH may be problematic for certain "special populations", such as patients with renal impairment, in whom impaired drug clearance may lead to excessive anticoagulation, and the elderly, who may have age-related reduced drug clearance or undiagnosed renal impairment. Weight-based dosing may also be problematic in obese patients. One the one hand, capping the dose as recommended by some regulatory agencies may lead to under dosing and reduced treatment efficacy; however, as intravascular volume does not have a linear relationship with body weight, weight-based dosing could also be excessive (2;3).

We were interested in determining the proportions of VTE patients in clinical practice who have special population characteristics or cancer, as treatment guidelines and dosing schedules are generally targeted to "usual" patients who may or may not constitute the majority of VTE patients. We performed a two-centre chart audit of the prevalence of special population characteristics (renal impairment, advanced age, obesity) and cancer among consecutive patients diagnosed with VTE in day to day practice, and assessed whether these characteristics appeared to influence the type and dose of anticoagulants prescribed to treat VTE.

METHODS

Medical records, emergency department records, thrombosis clinic charts, radiology reports and vascular lab reports from April 1, 2004 to March 31, 2005 were systematically searched to identify consecutive patients with objectively diagnosed acute VTE (deep venous thrombosis or pulmonary embolism) at two large university-affiliated hospitals in Montreal, Quebec and London, Ontario, Canada. Patients with calf muscle vein thrombosis or superficial vein thrombosis in the absence of deep vein involvement were not included.

Trained research assistants at each site abstracted patient records using study-specific case report forms. No patient identifiers were recorded on the case report forms and patients were entered into the study database using a study number. Data relevant to the study were recorded, including age, sex, serum creatinine and weight at the time of VTE diagnosis, presence and type of active cancer (defined as undergoing treatment for cancer, metastatic or terminal cancer, or if active cancer was specified in chart notes), site of VTE, type of anticoagulant initiated and dose of LMWH, where applicable. Thrombosis of the common femoral, superficial femoral and popliteal veins were considered as proximal deep vein thrombosis (DVT), and thrombosis of the posterior tibial, peroneal and anterior tibial veins were considered distal DVT.

The proportions of patients with renal impairment, advanced age, obesity and cancer were calculated, and the treatment prescribed for various patient subgroups was determined. Renal function was assessed using creatinine clearance (CrCl), which was calculated with the Cockcroft-Gault formula. Obesity was defined by total body weight, not body mass index, because data on patients' heights were not consistently available in the chart notes. Full dosing of LMWH was defined as prescription of a dose that was within ±10% of the manufacturer's recommended treatment dose. Comparisons between groups were performed using ANOVA

tests for means and chi square tests for proportions, as appropriate. A p value of <0.05 was considered statistically significant.

Prior to commencing this study, approval was obtained from the local Research Ethics Committees.

Role of funding source

The study sponsor had no role in the design and conduct of the study, the collection, management, analysis, interpretation and reporting of study data, the writing of the manuscript or the decision to submit the manuscript for publication.

RESULTS

A total of 524 patients (Montreal 293; London 231) with VTE were identified. Patient characteristics by study centre and in the two centres combined are summarized in **Table 1**.

Treatment of VTE

Overall, treatment prescribed for VTE consisted of LMWH and warfarin in 71% of patients, LMWH monotherapy in 13%, UFH plus warfarin in 4%, IVC filter alone in 4%, other in 5% (these included patients participating in research studies of experimental anticoagulants, or treatment other than first four categories) or no treatment (3%) (**Table 2**). Eight patients received an IVC filter along with anticoagulant treatment.

Special population characteristics and their influence on treatment

Renal impairment

Serum creatinine results dated close to the time of VTE diagnosis were available in the charts of 463 (88%) patients. While the mean calculated CrCl was 94.3 cc/min, less than half (48%) of patients had CrCl ≥90 cc/min, which is considered by the National Kidney Foundation (NKF) KDOQI Guidelines to represent normal renal function (i.e. NKF Stage I) (4). Mild renal impairment (CrCl 60-88 cc/min; NKF Stage II) was present in 27% of patients, moderate renal impairment (CrCl 30-59 cc/min; NKF Stage III) in 20% of patients and severe renal impairment (CrCl ≤30 cc/min: NKF Stages IV and V) was present in 5% of patients.

Patients who received UFH to treat VTE had lower mean CrCl than those who received LMWH (63.5 cc/min for UFH, vs. 96.2 cc/min for LMWH and warfarin and 95.4 cc/min for LMWH alone, p=0.003). However, an anticoagulant regimen that included LMWH was administered to 93% of patients with moderate renal impairment and 67% of patients with severe renal impairment, including the use of extended duration LMWH monotherapy in 13% and 13%, respectively. Among patients with moderate renal impairment, 89% received full dose LMWH while 11% received reduced dosing, with an average dose reduction to 78% of the full dose (range 60-89%). Among patients with severe renal impairment, 79% received full dose LMWH while 21% received reduced dosing; the average reduction in dose was to 78% of the full dose (range 73-82%).

Advanced age

While the study population had a mean age of 62.4 years (range 17-99), 31% of patients were greater than 75 years of age, 18% greater than 80 years of age and 3% older than 90 years of age. As was expected, renal function deteriorated with increasing age; patients younger than 75 years of age had the highest mean CrCl at 109 cc/min, while patients older than 75 years had

a mean CrCl of 56.2 cc/min, those over 80 years had a mean CrCl of 48.7 cc/min, and participants over 90 years of age had the lowest mean CrCl at 33.8 cc/min (**Figure 1**).

Mean age was significantly higher in patients who received UFH (70.3 yrs) or IVC filters (70.9 yrs) than those who received LMWH (61.5 yrs) (p=0.02, 0.04 respectively). Age did not influence dosing of LMWH (i.e. either under or over dosing in relation to recommended treatment dose).

Body weight

Body weight was documented in the chart in 499 (95%) patients. The mean weight of study participants was 79.6 kg. Seventy three (14.0%) patients weighed ≥100 kg (maximum 205 kg), while 26 (6.0%) patients weighed < 50 kg (minimum 35 kg).

Under dosing of LMWH by >10% was documented in 8% of patients who weighed < 100 kg compared with 36% of patients who weighed >100 kg (p<0.001), in whom the average prescribed dose was 78% (range 48%-87%) of the recommended dose for weight.

Active cancer

One hundred and thirty six (26%) patients had active cancer. Of these, 38.2% had metastatic disease at the time of VTE diagnosis. Although patients with active cancer were more likely to be treated with LMWH monotherapy that those without cancer (32% vs. 7%, p<0.001), less than one third of cancer patients received such therapy. Among patients with metastatic cancer, 41% were treated with LMWH monotherapy. Patients with active cancer who had lower extremity DVT or PE were more likely to be treated with LMWH monotherapy than those with isolated upper extremity DVT (35% vs. 18%, respectively).

DISCUSSION

LMWHs have more predictable anticoagulant activity than UFH and have been shown to be as effective as UFH for the prevention of recurrent VTE, with lower risks of bleeding, heparin-induced thrombocytopenia and osteoporosis (1;5). Due to their ease of administration and improved pharmacokinetic properties, LMWH have effectively replaced UFH for the treatment of acute VTE in most patients (1). LMWH are usually dosed according to patient weight and administered subcutaneously once or twice daily on an outpatient basis, but in certain patients (who we have termed 'special populations'), unmonitored weight-based dosing may be problematic.

This study aimed to determine the prevalence of special population characteristics among consecutive patients diagnosed with acute VTE at two hospital centers over a one year period. We found that such characteristics occurred frequently in our study population. Moderate or severe renal impairment was present in 25% of our patients, almost one third of patients were older than 75 years, and one in six weighed more than 100 kg. These results are relevant because VTE treatment guidelines and manufacturers' dosing schedules are primarily directed at the 'usual' patient with VTE, which assumes that the majority of patients with VTE do not fall into special population categories, and inappropriate dosing could be associated with risk of bleeding or lack of treatment efficacy. Furthermore, clinical trials which have informed treatment guidelines have usually excluded one or more of these special population groups, which leaves the practitioner somewhat challenged when faced with having to manage VTE in these patients.

In 12% of patients, a serum creatinine result dated close to the time of the acute VTE could not be located in the chart. However, we observed that renal function was significantly

poorer in patients who received UFH compared with LMWH, suggesting that clinicians take kidney function into consideration when prescribing anticoagulants. Nevertheless, we also found that a significant proportion of patients with moderate and even severe renal impairment received LMWH, including prolonged treatment with LMWH monotherapy, and that in the majority of these cases, no reduction in dose was prescribed. LMWHs are cleared by the kidneys, unlike UFH whose clearance is not exclusively renal (6). As a result, patients with impaired renal function who are treated with therapeutic doses of LMWH may experience excessive anticoagulation due to inefficient drug clearance and bioaccumulation and, as a result, an increased risk of major bleeding (7). Therapeutic doses of LMWH are generally considered to be contraindicated in patients with severe renal impairment, i.e. CrCl < 25-30 ml/min (6), although there appear to be differences among LMWHs with regard to drug accumulation in patients with renal impairment such that some compounds may have more favorable safety than others (3;8). In those with less severe renal impairment, monitoring of anti Xa levels is recommended if LMWH is used (6). In our study, we were not able to retrieve data on whether anti Xa levels were performed in patients with renal impairment who were prescribed LMWH, however use of anti Xa levels to monitor LMWH therapy is not routine practice at either of the two study centers, especially in patients prescribed only 5-7 days of LMWH, and the safety of using Xa activity levels to guide therapy has not been clinically validated. Use of UFH or LMWHs that do not bioaccumulate are likely to be better choices for patients with moderate or severe renal impairment.

Many of our patients were elderly or very elderly. Weight-based dosing of LMWH in the elderly could lead to excessive anticoagulation due to age-related impaired drug clearance or unrecognized renal impairment. In a recent multicenter registry study, patients >80 years had

significantly higher rates of major and fatal bleeding on anticoagulants than those <80 years, and the incidence of major bleeding was two-fold higher in elderly patients receiving long-term LMWH than those receiving oral coumarin (9). As serum creatinine levels generally overestimate renal function in the elderly due to their reduced muscle mass (4), calculation of CrCl to detect renal impairment that might necessitate LMWH dose reduction is especially relevant in this patient group.

We found that 36% of patients weighing >100 kg who received LMWH were under dosed by 10% or more. Under dosing of obese patients has also been reported by others (10). While obese patients who are under dosed due to labeling imposed maximum dosage or capped dosing systems may experience reduced treatment efficacy, it has also been suggested that weight-based dosing may in fact be excessive because LMWHs are not distributed in fat and the relationship between body weight and intravascular volume is not linear (2;6). While it has been suggested that periodic monitoring of anti-Xa levels in obese patients should be considered (6), studies of obese patients dosed with LMWH according to body weight have shown that anti-Xa activity is not increased to supratherapeutic levels (2;6;11) and the incidence of major bleeding does not appear to be elevated (6;12). Establishing clear guidelines for the treatment of obese VTE patients is important, as obesity is a significant risk factor for VTE.

The strong association between cancer and VTE has long been known to exist. While we did not consider cancer patients to be a 'special population group' per se, we were interested in assessing how VTE was managed in cancer patients since current treatment guidelines recommend that treatment of cancer patients with lower extremity DVT or PE should consist of LMWH monotherapy for at least 6 months, and it has been increasingly recognized that gaps exist between knowledge and practice in the implementation of VTE treatment guidelines in day-

to-day clinical practice (13). One quarter of our VTE patients had active cancer and of those with lower extremity DVT or PE, only 35% received such therapy. Due to our study's retrospective design, the reasons for this low rate could not be ascertained but could include high cost or perceived inconvenience of daily LMWH injections, or that the interval between the publication of key trials and subsequent expert recommendations (1;14) and the initiation of our study was too short to elicit consistent uptake of this evidence into clinical practice.

We recognize that our study has several limitations. Its retrospective design increases the likelihood of missing or incorrect data; for example, weight was not always documented in the chart and height was virtually never available, hence BMI could not be calculated. Patients were considered not to have cancer if no mention of cancer was made in the patient chart, which may have led to underestimation of the prevalence of cancer or other clinical characteristics in our population. Although we screened multiple sources (e.g. vascular laboratory logs, medical records, emergency department logs, clinic appointment sheets) to identify patients diagnosed with VTE during the study time window, some VTE patients may have been overlooked. As this study was not designed to address the safety or efficacy of different treatments or treatment doses, we are unable to comment on associations between treatments or doses and clinical outcomes such as bleeding or recurrent VTE in various patient groups. Finally, as the two participating study centers are tertiary referral centers with considerable experience in managing VTE, our results might not be fully generalizable to other hospital centers.

In conclusion, in clinical practice, renal impairment, advanced age, obesity and cancer are frequently present in patients with VTE. A considerable proportion of patients with these features may not receive the optimal type or dose of medication to treat VTE. Future publications should seek to clarify dosing recommendations for special population groups and

further research should address gaps between knowledge and practice in the implementation of VTE treatment guidelines in day-to-day clinical practice.

Table 1. Patient characteristics

	Montreal	London	TOTAL
Number of patients	293	231	524
Mean age (years)	66.2	57.5	62.4
Males, %	48%	46%	47%
Mean weight (kg) (n=499)	76.5	83.2	79.6
Mean creatinine clearance (cc/min) (n=463)	90.2	98.5	94.3
VTE diagnosis; n (%)[1] :			
PE	35 (12%)	64 (28%)	99 (19%)
Arm DVT	2 (1%)	41 (18%)	43 (8%)
Leg DVT [2]	281 (96%)	133 (58%)	414 (79%)
Highest level: Proximal	167 (61%)	132 (99%)	296 (73%)
Highest level: Distal	109 (39%)[*]	1 (1%)[#]	110 (27%)
Cancer status; n (%):			
History of cancer diagnosis	104 (36%)	69 (30%)	173 (33%)
Active cancer	81 (28%)	55 (24%)	136 (26%)

Table 1, Notes:
[1] Percents add up to more than 100% as some patients had concurrent DVT and PE
[2] Data on highest level missing for 5 Montreal patients
* Whole leg ultrasound is routinely performed for suspected DVT
[#] Proximal vein only ultrasound is routinely performed for suspected DVT

Table 2. Treatment of venous thromboembolism

	Montreal	London	Total
LMWH, warfarin	183 (63%)	186 (81%)	369 (71%)
LMWH alone	42 (15%)	28 (12%)	70 (13%)
UFH, warfarin	23 (8%)	0 (0)	23 (4%)
IVC filter	20 (7%)	0 (0)	20 (4%)
Other	9 (3%)	16 (7%)	25 (5%)
No treatment	13 (5%)	1 (0.04)	14 (3%)

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Figure 1. Mean creatinine clearance by age cut-off