Multicentre hospital drug utilization study on the prophylaxis of venous thromboembolism

The Venous Thromboembolism Study Group of the Spanish Society of Clinical Pharmacology*

Coordinating Centre and Data Analysis: JOAN ANTONI VALLÈS, ANTONI VALLANO, FERRAN TORRES, JOSEP MARIA ARNAU & JOAN-RAMON LAPORTE

Servei de Farmacologia, CSU Vall d'Hebron; Unitat de Farmacologia Clínica, Universitat Autònoma de Barcelona, Spain

- 1 Thromboembolic disease (TED) is an important cause of in-hospital morbidity and mortality. Although different prophylactic approaches have been shown to be effective and cost-effective, surveys have suggested that they are underused. The aim of this study was to estimate the prevalence of use of TED prophylaxis in our hospitals.
- 2 All patients admitted on a specified day to the Internal Medicine and General Surgery wards of seven Spanish university hospitals were included in the study. They were identified cross-sectionally and followed up until discharge or for 15 days. Information about the following variables was collected: risk factors for venous thromboembolism, prophylactic measures used (if any), contraindications to the use of each specific drug or other prophylactic measure, and dosage schedule of the drug used, if any.
- 3 Nine hundred and thirty-nine patients (53% men) were studied. The most common risk factors for venous thromboembolism were: age ≥ 40 years (802; 85%), major surgery (298; 32%), immobilization ≥ 6 days (285; 30%), obesity (241; 26%), and cancer (202; 22%).
- 4 Prophylactic measures were used in 320 patients (34%). Of these, 297 (93%) received heparin, mainly as low molecular weight heparins (248, 78%); physical measures were rarely used.
- 5 Five hundred and eighty-three patients (62%) fulfilled criteria for moderate or high risk of venous thromboembolism; only 275 (47%) of them received any form of prophylaxis.
- 6 In a multivariate analysis the following variables were associated with the use of prophylaxis: hospital centre (adjusted odds ratios, 1.7 to 23.3, compared with reference hospital), history of venous thrombosis, major surgery, congestive heart failure, inflammatory bowel disease, age, immobilization, dehydration, and obesity.
- 7 Contraindications to the use of anticoagulant or antiplatelet drugs were present in 234 patients (25%), but no relationship to the use of heparin was found. Of the patients treated with heparin who underwent major surgery, only 55 (36%) had received a preoperative dose.
- 8 Although prophylaxis of TED was associated with certain risk factors, it was highly underused in moderate and high risk patients. Wide interhospital variability in the use of prophylaxis was recorded; this variability persisted after adjusting for differences in the prevalence of risk factors and for the presence of contraindications in each centre. Low molecular weight heparins are replacing conventional unfractionated heparin for this indication.

Keywords thromboembolism, prevention pulmonary embolism, prevention surgery drug utilization heparin heparin, low molecular weight

Correspondence: Dr Joan-Ramon Laporte, Servei de Farmacologia Clínica, CSU Vall d'Hebron, 08035 Barcelona, Spain

*Participating centres: Hospital Universitari Germans Trias i Pujol, Badalona: J. COSTA, J. A. GARCÍA, C. VEDIA; Hospital Universitari del Mar, Barcelona: M. FARRÉ, M. TERÁN; Hospital Universitario Virgen de la Macarena, Sevilla: J. A. DURÁN, R. RAVELLA; Hospital Universitario Virgen del Rocío, Sevilla: J. L. PÉREZ, J. R. CASTILLO, J. TORELLÓ; Hospital Universitario Virgen de la Victoria, Málaga: M. CABELLO, J. A. GONZÁLEZ, M. LUCENA; Hospital Clínico Universitario San Carlos, Madrid: E. VARGAS, L. LÓPEZ, A. GIL

Introduction

Thromboembolic disease (TED) is an important cause of morbidity and mortality among hospital inpatients [1]. Screening for asymptomatic thrombosis has been advocated to prevent pulmonary embolism, but is not cost-effective [2]. The most efficient way to prevent TED is routine prophylaxis in moderate and high risk patients [3–5]; some studies have shown that such prophylaxis is also cost-effective [6–8].

Despite this evidence and despite recommendations of national consensus groups on the use of prophylaxis [9, 10], recent surveys have suggested that prophylaxis is little used [11, 12], and a high incidence of venous thromboembolism is still found at autopsy [14]. As the magnitude of the use of TED prophylaxis in the hospital setting in our country was unknown, the Spanish Society of Clinical Pharmacology performed a national multi-centre study to assess when and how prophylaxis for venous thromboembolism is used.

Methods

Data from seven hospitals were collected: Hospital Universitari Germans Trias i Pujol, Badalona; Hospital Universitari del Mar, Barcelona; Hospital Universitario Virgen de la Macarena, Sevilla; Hospital Virgen del Rocío, Sevilla; Hospital Universitario Virgen de la Victoria, Málaga; Hospital Clínico Universitario San Carlos, Madrid and Hospital Universitari Vall D'Hebron, Barcelona. The study was cross-sectional and prospective. Patients admitted to Internal Medicine and General Surgery Services on May 12, 1992 were included. Patients admitted to other medical or surgical wards were excluded, as were those receiving anticoagulants for established venous thrombo-embolism.

The following data were recorded and abstracted from the medical records: age, sex, surgical operations, its duration and kind of anaesthesia, previous episodes of deep vein thrombosis or pulmonary thromboembolism, immobilization for 6 days or more, height and weight, cancer, non-haemorrhagic stroke with paralysis of lower limbs, congestive heart failure, inflammatory bowel disease, nephrotic syndrome, polycythaemia, recent use of high dose oestrogen therapy, thrombophilia, chronic obstructive pulmonary disease, and major trauma. The following information on the main study variables was also collected: type of prophylaxis used, if any (unfractionated heparin, low molecular weight heparin, oral anticoagulant, dextran, graduated elastic compression stockings, intermittent pneumatic compression devices, and combinations of them), dosage schedule if a drug was used, contraindications to the use of anticoagulants (haemorrhagic disorder or diathesis, potentially bleeding lesions, recent cerebrovascular accident, recent central nervous system, spinal cord or eye trauma or surgery, chronic renal failure, severe hypertension, pregnancy, aortic aneurysm, allergy to heparin and infective endocarditis). Patients were followed up until discharge or for 15 days.

Moderate and high risk patients were defined as those in one of the following categories: (a) major surgery (>30 min) plus another general risk factor (see below); (b) immobilization for 6 days or more plus another general risk factor; (c) major trauma plus another general risk factor, and (d) three or more general risk factors. General risk factors were age ≥ 40 years, obesity, varicose veins or deep vein insufficiency, pregnancy, puerperium, high dose oestrogen therapy, stroke, previous deep vein thrombosis or pulmonary embolism, thrombophilia, dehydration, malignancy, chronic respiratory insufficiency, heart failure, cardiomyopathy, recent myocardial infarction, constrictive pericarditis, generalised oedema, extensive burns, paralysis of lower limbs, sepsis, inflammatory bowel disease, nephrotic syndrome, polycythaemia, paraproteinaemia, paroxysmal nocturnal haemoglobinuria, Behcet's disease, and homocystinuria [9, 10, 12]. A subset of high risk patients was defined as those who presented with (1) fracture or major orthopaedic surgery of pelvis, hip, or lower limb (these were patients transferred from the Orthopaedic service because they had medical complications arising before or after orthopaedic surgery); (2) major surgery in patients with malignancy; (3) major surgery, trauma, or illness in patients with previous deep vein thrombosis, pulmonary embolism, or thrombophilia; (4) lower limb paralysis (for example, hemiplegic stroke, paraplegia), and/or (5) major lower limb amputation. Moderate risk patients were those in categories a, b, c or d (above), but without any of these 5 risk factors.

Statistical analyses were performed using Pearson χ^2 -test and multivariate analysis, using SPSS-x and BMDP software.

Results

On the day of data collection 970 patients were admitted to the wards included in the study. Thirty-one were excluded because they were on anticoagulant treatment, leaving 939 patients (497 men, 53%). Their median age was 64 years (range 13–98). The most prevalent risk factors for TED were age ≥ 40 years (802 patients, 85%), major surgery (298, 32%), immobilization ≥ 6 days (285, 30%), obesity (241, 26%), cancer (202, 22%), and heart failure (135, 14%) (Table 1). The median number of risk factors per patient was 3 (range 0–9).

Table 1 Presence of risk factors

<i>Risk factor</i>	<i>n</i>	<i>(%)</i>
Age ≥ 40 years	802	(85)
Major surgery	298	(32)
Immobilization	285	(30)
Obesity	241	(26)
Malignancy	202	(21)
Heart failure	135	(14)
Pulmonary failure	121	(13)
Stroke	53	(6)
Cardiomyopathy	44	(5)
Other	196	(20)

Table 2 Basic characteristics of the different hospital populations

Variables	Hospital							Total	P value
	1	2	3	4	5	6	7		
Number of patients (n)	65	55	183	169	134	146	187	939	
Prevalence of TED prophylaxis measures	78%	40%	23%	12%	25%	54%	39%	34%	<0.00001
Prevalence of contraindications to the use of anticoagulant drugs	5%	7%	29%	28%	24%	42%	18%	25%	<0.01
Moderate- and high-risk patients	75%	49%	68%	48%	48%	75%	68%	62%	<0.00001
Prevalence of TED prophylaxis measures in risk patients	94%	78%	30%	18%	39%	62%	50%	47%	<0.00001
Prevalence of contraindications to the use of anticoagulant drugs in risk patients	2%	11%	33%	34%	23%	47%	19%	28%	<0.00001

Prophylaxis of TED was used in 320 patients (34%). Heparin was used in 297 of them (93%). Two hundred and thirty-four patients (25%) had some contraindication to the use of anticoagulants, although in most of them (154, 16%) the contraindication was relative. Prophylactic physical measures were used only in 17 patients (1.8%; range according to hospitals 0%–5.5%). There were statistically significant interhospital differences in the prevalence of TED prophylaxis measures (range 12–78%, $P < 0.00001$) and in the prevalence of contraindications to the use of anticoagulant drugs (range 4.6–42%, $P < 0.01$) (Table 2). Low molecular weight heparins were most often prescribed (248 patients, 78%) —enoxaparin was given to 127 patients, tedelparin to 83, and nadroparin to 38; 49 patients (22%) received calcium heparin. The median duration of heparin prophylaxis was 10 days (range 1–160 days). Out of 298 patients who underwent major surgery, only 159 (53%) received prophylaxis (153 with heparin), and of these, only 55 (36%) received a preoperative dose. Five hundred and eighty-three patients (62%; 297 men and 288 women) fulfilled criteria for moderate or high risk of developing TED (Table 3). Their median age was 67 years (range 13–98). The proportions of these patients showed significant interhospital variability (range 48–75%, $P < 0.00001$). Out of these 583 at risk patients, only 277 (48%) received prophylaxis (Table 3), although contraindications to the use of anticoagulants were present in 163 (28%). The use of prophylaxis in this subgroup showed significant interhospital differences (range 18–94%, $P < 0.00001$); the presence of contraindications to the use of anticoagulants also showed wide interhospital variability (range 2–47%, $P < 0.00001$) (Table 2).

In a multivariate analysis, the following variables were associated with the use of prophylaxis in the whole study population: hospital, previous venous thrombosis, major surgery, congestive heart failure, inflammatory bowel disease, age, immobilization, dehydration and obesity (Table 4). In the moderate and high risk subgroup the variables associated with the use of prophylaxis were mostly the same: hospital, previous venous thrombosis,

Table 3 Risk of venous thrombosis and use of prophylaxis

Risk degree	Patients		Prophylaxis	
	n	(%)	n	(%)
Low	356	(38)	43	(12)
Moderate ^a	428	(45)	188	(44)
High ^b	155	(17)	89	(57)
Total	939	(100)	320	(34)

Pearson $\chi^2 = 69.3$ ($P < 0.00001$).

^aSubcategories (see **Methods**): a, $n = 23$; b, $n = 31$; c, $n = 1$; d, $n = 117$; a + b, $n = 6$; a + d, $n = 90$; b + d, $n = 109$; c + d, $n = 1$; a + b + d, $n = 47$; a + c + d, $n = 1$; b + c + d, $n = 2$.

^bSubcategories (see **Methods**): 1, $n = 10$; 2, $n = 83$; 3, $n = 5$; 4, $n = 53$, and 5, $n = 4$.

Table 4 Factors associated with the use of prophylaxis

	Adjusted OR	95% CI
Hospital 1	23.3	9.9–55.1
Hospital 2	5.9	2.5–13.7
Hospital 3	1.7	0.9–3.4
Hospital 4	1.0 ^a	
Hospital 5	2.7	1.3–5.6
Hospital 6	8.8	4.5–17.1
Hospital 7	3.6	1.9–6.8
Previous venous thrombosis	5.9	1.6–21.7
Major surgery	5.2	3.6–7.5
Congestive heart failure	3.0	1.8–4.8
Inflammatory bowel disease	2.9	1.4–6.2
Age (40 years or more)	2.3	1.3–4.1
Immobilization	2.3	1.6–3.2
Dehydration	2.0	1.2–3.2
Obesity	1.7	1.2–2.4

^aReference category.

major surgery, congestive heart failure, cardiomyopathy, immobilization, respiratory failure, and obesity. We did not find any relationship between the use of prophylaxis and the presence of malignancy. Similarly, there was no relationship between the presence of contraindications to the use of anticoagulants and their use for prophylaxis of TED.

Discussion

The results of this study show that there is a large underuse of prophylaxis for TED. This is especially significant among patients with moderate or high risk for developing TED, for whom a strong consensus exists about its effectiveness [2, 6] (prophylaxis was used in 47% of them). Our data suggest that the reason for this underuse is not related to the presence of contraindications to anticoagulants.

In the few studies on the topic which have been published up to now, a wide variability in the use of this prophylaxis has been documented. A hospital-based American study showed a low use of prophylaxis [12], whereas in an opinion survey carried out among British orthopaedic surgeons, most of them (90%) stated that they used prophylactic measures [13]. In contrast with these surveys, our study was a prospective one, and therefore we were able to obtain more accurate information on certain variables.

Among the different factors considered in our study, the hospital has been the most strongly associated with TED prophylaxis. Anderson *et al.* [12] noted in their study that teaching hospitals performed more prophylaxis than the other centres. All the centres included in our study were teaching hospitals. The large interhospital differences recorded in our study may be related to differential levels of motivation, to different working strategies (integration between medical and surgical groups, more or less clinical-oriented haematologists, different influences of the Clinical Pharmacology Service), and to varying degrees of influence of the manufacturers of low molecular weight heparins.

Heparins were the most widely used method of prophylaxis, mainly as low molecular weight heparins. Non-pharmacological methods with proven efficacy (intermittent pneumatic compression, graduated elastic compression stockings) were hardly used at all. The

reasons for their underuse could be their high cost and the discomfort experienced by many patients, who cannot tolerate them. In our country there is no tradition of using these physical measures. Finally, the low proportion of operated patients receiving a preoperative dose of heparin (36%), in spite of the evidence supporting its effectiveness [3, 4, 15–18], is also notable. This sub-optimal use may be related to surgeons' fear of haemorrhage, which seems to be largely unwarranted [19].

In the present study some factors associated with the use of TED prophylaxis were similar to those found in Anderson's study [12], namely the hospital, a history of venous thromboembolism, major surgery, congestive heart failure, age and obesity. In our study, however, we found an association of TED prophylaxis with immobilization which was not recorded in the American study. This may be due to the different design we used: we collected data on all patients daily until discharge, and the information may be more accurate than that obtained retrospectively from medical records.

Malignancies were not associated with use of TED prophylaxis; this is especially worrying in view of the great importance of abdominal cancers as a risk factor for thromboembolic complications [10].

Analysis of moderate and high risk subgroups of patients showed that the factors related to the use of prophylaxis were similar to those in the whole study population.

In conclusion, we have documented a substantial underuse of prophylaxis against thromboembolic disease in patients admitted to Internal Medicine and General Surgery Services of teaching hospitals in our country. This underuse is especially worrying among high and moderate risk patients. Our results underline the need to develop a multidisciplinary intervention strategy, with the aim of optimizing the practical approach to this common clinical problem and of evaluating its effectiveness in daily clinical practice.

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