



Outpatient treatment of community acquired venous thromboembolism - the Christchurch experience

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Abstract

Aims To describe our experience with the outpatient treatment of venous thromboembolic disease at Christchurch Hospital in the first 30 months following the establishment of an outpatient haemostasis service in March 1999.

Methods Patient clinical and laboratory data were collected prospectively on a Microsoft Access database and statistical analyses were performed using Microsoft Excel software.

Results 288 patients were treated and their medical profiles are detailed. The treatment protocols for low molecular weight heparin and warfarin, using dosing protocols determined by weight and INR results, are described. During the course of heparin therapy no patient had clinical progression of thrombosis and only one had haemorrhage.

Conclusions Treatment of DVT delivered to outpatients has proven to be effective and safe.

Heparin therapy, followed by oral anticoagulation has been routine treatment for deep venous thrombosis (DVT) for many years. Usually standard unfractionated heparin was administered by intravenous infusion and monitored by activated partial thromboplastin time (APTT) testing. This required the patient to be in hospital until oral anticoagulation became established. More recently, low molecular weight heparin has been available and given subcutaneously, on a weight-determined dose without monitoring, results in predictable anticoagulation. This is at least as safe and effective as unfractionated heparin in the treatment of DVT and pulmonary embolism (PE)^{1,2}. Trials have also shown that such treatment can be given safely out of hospital^{3,4}. Outpatient anticoagulation for initial treatment of DVT and related disorders began at Christchurch Hospital in March 1999. This report details our experience of treating patients over the following 30 months and includes a report on the use of an oral anticoagulation dosage protocol.

Methods

The Haemostasis Service at Christchurch Hospital was established to provide outpatient care for adults with bleeding and clotting disorders, principally those with haemophilia or venous thrombosis. It consists of a haemostasis nurse (full time) and a haemostasis physician/haematologist (part time). Most patients with DVT were seen initially in the Emergency Department, diagnosed by ultrasound, and then assessed by the Internal Medicine Acute Team. If they had no other significant illness requiring admission they were referred to the Haemostasis service for further management. Patients arriving during normal working hours were often referred immediately. Those arriving out of hours received an initial dose of low molecular weight heparin and were referred to the clinic the following morning. Some patients with extensive superficial thrombophlebitis or with non-massive PE were also referred to the clinic.

Table 1. Dosing schedule for dalteparin and warfarin.

DALTEPARIN DOSAGE		
WEIGHT (kg)	DOSE (u/day)	DOSE/KG
44-55	10,000	227-182
56-67	12,500	223-186
68-80	15,000	220-187
81-99	18,000	222-182
100-110	20,000	200-181
WARFARIN DOSAGE		
		DOSE (mg/day)
DAY 1	WEIGHT ≥ 60 kg	
	INR ≤ 1.2	15 mg
	WEIGHT < 60 kg	
DAY 2	INR ≤ 1.2	10mg
	INR > 1.2	Treat empirically
	INR ≤ 1.5	5mg
DAY 3	INR > 1.5	0mg
	INR < 1.5	10mg
	INR 1.5-1.9	5mg
	INR 2.0-2.5	4mg
DAY 4	INR 2.6-3.0	3mg
	INR > 3.0	0mg
	INR < 1.5	10mg
	INR 1.5-1.9	8mg
	INR 2.0-2.5	5mg
DAY 5	INR 2.6-3.0	3mg
	INR > 3.0	0mg
	INR < 2.0	10mg
	INR 2.0-2.2	8mg
	INR 2.3-2.4	6mg
	INR 2.5-2.6	4mg
	INR 2.7-3.0	2mg
	INR > 3.0	0mg

The patients were seen daily by the haemostasis nurse and at least once by the haemostasis physician. They received daily subcutaneous injections of dalteparin (Fragmin) on a weight-based schedule (Table 1) with a maximum dose of 20000iu. Warfarin therapy was commenced the same day as the heparin or the following day and was administered according to a nomogram (Table 1) modified from one devised by Fennerty and colleagues.⁵ The Fennerty protocol was modified (a) to have a weight-determined dose on day 1, (b) to have a lower dose day 2, (c) to have a zero dose if INR >3 and (d) to have fewer steps. Patients who had commenced warfarin off protocol prior to referral or whose initial INR was elevated were dosed empirically. Patients with superficial thrombophlebitis were treated with therapeutic doses of dalteparin for two weeks without the addition of warfarin.

Patient history and examination were recorded on a standard form and the following tests were routinely performed: prothrombin time (PT), APTT, blood count, ESR, creatinine, liver function tests, D-dimers (SimpliRED screening test or IL D-dimer assay), thrombophilia screen (antithrombin, protein S, protein C, activated protein C (APC) resistance, plasminogen, lupus anticoagulant–genetic tests for Factor V Leiden and the G20210A prothrombin mutation were performed if the APC resistance test was positive), chest X-ray and ECG. Prostate specific antigen (PSA) was performed in males aged over 40 years and pelvic ultrasound in females.

The patients were monitored daily with clinical assessment of legs and pulse oximetry. Low molecular weight heparin was given for at least five days and until the INR was ≥2.0 on two consecutive days. Blood was taken for INR testing, warfarin tablets were provided and the patient was phoned later that day with warfarin dose advice. The patients were discharged to their general practitioner once oral anticoagulation was stable with a recommendation for the duration of therapy and DVT patients were offered a review at the clinic in one year's time. Those who attended that clinic were assessed for history of clinical recurrence of venous thromboembolism (VTE) and for development of the post-

phlebotic syndrome. The patient data were collected in the hospital notes and on a Microsoft Access database and statistical analysis was performed using Microsoft Excel software.

Results

Prior to starting the DVT outpatient service in March 1999, about 100 patients were admitted annually to the Christchurch hospital for treatment of community acquired DVT. In the first two and a half years of the outpatient service, we treated 228 patients with VTE. During that same period another 49 patients were admitted for inpatient care and 24 of those were in the first four months showing that the majority of patients were managed by the outpatient service.

Table 2. Age/sex of patients and site of thrombi.

Male	124	
Female	104	
Age (male)	21-80	53.1 (mean)
Age (female)	16-90	54.5 (mean)
Upper limb DVT	10	
Upper limb Superficial VT	5	
Lower limb DVT	173	
Iliac		9
Femoral		79
Popliteal		60
Calf		25
Lower limb Superficial VT	12	
Pulmonary embolism	28	

There were 228 patients (124 male, 104 female) aged 16 to 90 years with a mean of 53.8 years (Table 2) who were treated by the outpatient Haemostasis Service during this period. The primary diagnoses were lower limb DVT (173) (right 70, left 103), upper limb DVT (10), superficial vein thrombosis (17) and pulmonary embolism (28). 60 patients had suffered a prior venous thrombosis.

Table 3. Risk factors for thrombosis.

CLINICAL RISK FACTORS	N	% of patients
Previous venous thrombosis	60	26.3
Family history of VTE	42	18.4
Travel >4 hrs within last 4 weeks	34	14.9
Recent surgery	34	14.9
Active malignancy (6 months)	22	9.6
Immobility	20	8.8
Leg trauma	16	7.0
Oral contraceptive use	15	6.6
Hormone replacement Rx	8	3.5
IV central line	8	3.5
THROMBOPHILIA		% of patients tested
Factor V Leiden (hetero)	36	18.3
Protein S deficiency	11	5.6
Lupus anticoagulant	4	2.0
Protein C deficiency	3	1.5
Antithrombin deficiency	2	1.0
Prothrombin mutation (hetero)	1	2.8

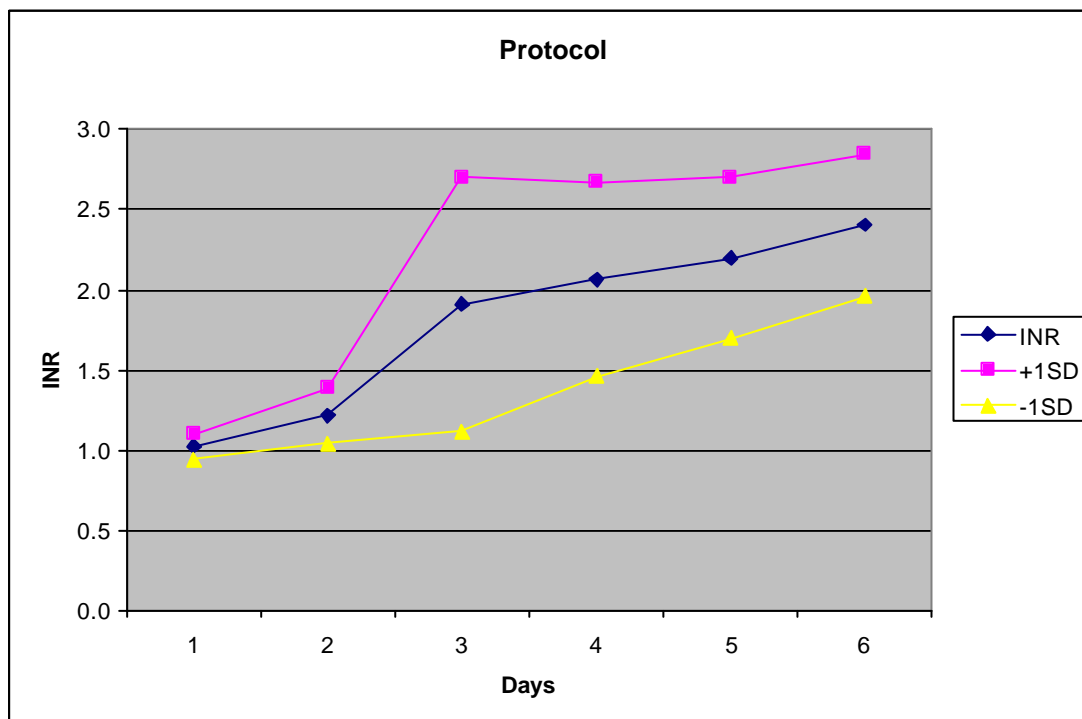
128 patients had one clinical risk factor, 57 had two, five had three or more and 38 had no recognisable clinical risk factor (Table 3). Of the 34 patients with recent surgery, 20 had orthopaedic procedures. 22 patients had active cancer, or cancer diagnosed or treated within the last six months. No new cancers were diagnosed at presentation. Thrombophilia tests were performed in 197 patients and the results appear in Table 3.

Table 4. D-dimer result and site of thrombus.

SITE OF THROMBUS	Positive	Negative	Not tested
Upper limb DVT	5	0	5
Upper limb Superficial VT	2	1	2
Lower limb DVT			
Iliac	7	0	2
Femoral	49	5	25
Popliteal	34	12	14
Calf	11	4	10
Lower limb Superficial VT	9	0	3
Pulmonary embolism	20	2	6

At the beginning of this 30 month period, D-dimers were assessed as either positive or negative by the SimpliRED test and more recently quantified by IL D-dimer assay (>250mg/L considered elevated/positive). 161 of the patients were tested for D-dimers before receiving any heparin and only these results were analysed (Table 4). Of those with pulmonary embolism or iliac or femoral DVT, 92% had positive D-dimers whereas only 74% of those with popliteal or calf vein thrombosis had elevated levels. Of the eight upper limb thrombi tested, seven had elevated levels and all nine lower limb superficial vein thrombi tested had elevated levels.

Figure 1. INR results (+/- 1SD) in protocol patients.



135 patients followed the warfarin dosing protocol. The mean doses of warfarin were 14.6 (day 1), 4.9 (day 2), 5.5 (day 3), 6.2 (day 4), 6.6 (day 5) and 5.8 (day 6). The mean INRs were 1.0 (day 1), 1.2 (day 2), 1.9 (day 3), 2.1 (day 4), 2.2 (day 5) and 2.4 (day 6) (Figure 1). There were 29 INR results over 3 during the first six days of treatment (3.6% of tests). The mean duration of heparin therapy in this group was 5.8 days.

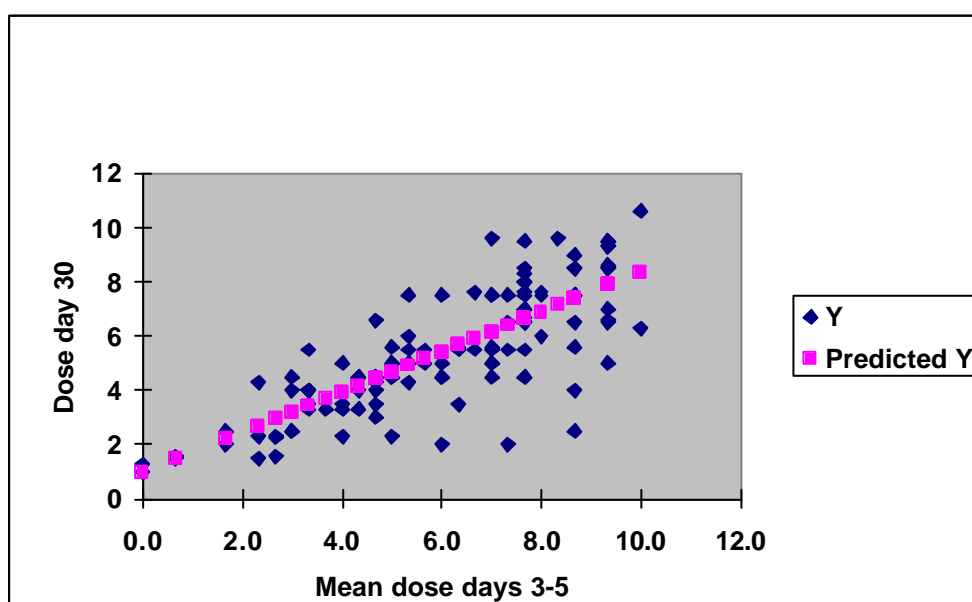
Patients in different age and weight groups achieved comparable degrees of anticoagulation using our dosing protocol though this was achieved with different doses of warfarin (Table 5).

Table 5. Warfarin dose (mg/day) and INR by age and weight of patient.

GROUP	MEAN AGE (years)	MEAN WEIGHT (Kg)	MEAN WARFARIN		MEAN INR DAY 5
			DOSE	DAY 5	
Age < 70	48	85	6.9		2.2
Age 70+	76	74	4.7		2.5
Wt <60 Kg	56	54	4.7		2.6
Wt 60-79 Kg	51	72	6.1		2.2
Wt 80-99 Kg	52	88	7.1		2.2
Wt 100+ Kg	52	110	7.7		2.1

The relationship was assessed between the mean warfarin dose on days 3-5 (using protocol-determined doses) and the maintenance warfarin dose on day 30 obtained by phone call to the patient's general practice clinic (Figure 2). There was a positive correlation ($R^2 = 0.62$ $p < 0.001$) and line of best fit was $y = 0.969 + 0.739x$.

Figure 2. Correlation of mean warfarin dose days 3-5 with maintenance dose day 30 in protocol patients only.



76 patients received empirical warfarin dosing. The mean doses of warfarin were 9.6 (day 1), 6.6 (day 2), 5.6 (day 3), 5.6 (day 4), 6.5 (day 5) and 6.5mg (day 6). The mean INRs were 1.1 (day 1), 1.2 (day 2), 1.9 (day 3), 2.1 (day 4), 2.1 (day 5) and 2.2 (day 6). There were 20 INR results over 3 during the first six days of treatment (4.4% of tests). The mean duration of heparin therapy in this group was 6.5 days. Seventeen

patients (including eleven with superficial vein thrombosis) received no warfarin and were treated with heparin only.

No patients suffered clinical pulmonary embolism or extension of DVT during the low molecular weight heparin treatment. Only one patient suffered a haemorrhage during this time. This was a 68 year old woman with an INR of 2.1 on day three who developed epistaxis which persisted despite reversal of anticoagulation and required surgical management.

117 DVT patients were diagnosed more than one year prior to the end of the study period and theoretically were eligible for a one-year clinical review. Only 63 attended. Reasons for non-attendance included: failure to receive booking advice, failure to attend, non-residence in Christchurch and death. Three patients were known to have had a recurrence of DVT within the first year. The Patient Management System (PMS) records of the other 54 patients were accessed to identify if any had been admitted to a public hospital for recurrent VTE but none had. Five patients are known to have died within the year following diagnosis of DVT. All died of cancer at 0.3, 1,1,3 and 9 months following DVT and all but one were known to have cancer when the DVT occurred. Twelve of the 63 patients reviewed at one year had developed mild (none severe) post phlebotic syndrome using the criteria of Prandoni et al.⁶

Discussion

Christchurch Hospital is the only hospital in the city that accepts acute general medical admissions. During the study period most cases of suspected DVT in the community were sent to this hospital for diagnosis and subsequent treatment.

The prevalence of laboratory and clinical prothrombotic states was as expected (Table 3). Height was not routinely recorded in these patients hence obesity was not formally assessed. Although obesity is often considered a risk factor for spontaneous DVT, this has been challenged.⁷ The most common inherited condition was factor V Leiden, found in 18% of those tested. Further cases of the prothrombin mutation would probably have been detected if more patients had been tested for that genetic mutation. The extent to which thrombophilia testing should be done and how the results should influence patient management remains somewhat controversial.⁸ Although most of our patients were tested for thrombophilia, the results rarely influenced our management. Based on the reported high recurrence rate in such people,⁹ the patient with heterozygosity for both factor V Leiden and the prothrombin mutation was advised to take prolonged warfarin therapy but chose not to follow that advice.

Recommended schedules for dalteparin dosing had placed a daily upper limit of 18000u as this had been used in initial clinical trials. As there is evidence that the pharmacokinetics of low molecular weight heparin are not significantly altered in obese subjects,¹⁰ we extended this upper limit to 20000u thus allowing a standard weight-based dosing schedule for patients weighing up to 110kg (Table 1).

Traditionally warfarin therapy was started with a loading dose. Most patients using the Fennerty protocol receive 10 mg on both day one and day two and this dose was commonly used in our hospital. As the mean maintenance dose is about 6mg, a "10,10" protocol constitutes a loading dose on both day 1 and day 2 for most people. If a loading dose is to be used, it seems more logical to give that on day 1 only and 15mg was chosen for those >60Kg and 10mg for 60+Kg.¹¹ Because of concern with

early over-anticoagulation and low factor VII levels with high initial doses, loading doses are now less frequently used and a starting dose of 5mg is favoured. A study of 53 patients given an initial dose of either 5mg or 10mg demonstrated a similar time to achieving a therapeutic INR in both groups.¹² In that study, 4% of INR results in the first six days of treatment were above 3 in the 5mg group compared to 12% in the 10mg group. In our protocol patients, 3.6% of the tests were above 3 in the same time period and in our non-protocol group 4.4% of the tests were above 3. Our patients were not randomly allocated to protocol or non-protocol so no formal comparison can be made between the groups. The results, however, suggest that the use of our protocol, including the use of a loading dose, can accommodate the differing dose requirements associated with varying age and weight (Table 5) without an excess of over anticoagulation.

No analysis of the cost of this service compared to the cost of alternative inpatient care was made for the purposes of this paper. We believe, however, that the economic benefits observed elsewhere would apply.¹³ A previous paper in this Journal documented some deficiencies in the transfer of warfarinised patients from Christchurch hospital to general practitioner care.¹⁴ We expect that the more formalised transfer protocol, accompanied by treatment recommendations, used by our service will improve patient care during and following this transition. Although no formal evaluation of patient satisfaction was performed, the number of spontaneous complimentary statements made about the service impressed us. In particular, the patients were pleased to be out of hospital and few found difficulty with daily transport. The objective results of the first 30 months activity of this clinic confirm that treatment of VTE can be provided effectively and safely in the outpatient setting.

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