Prophylaxis of deep-vein thrombosis in fractures below the knee

A PROSPECTIVE RANDOMISED CONTROLLED TRIAL

D. P. Goel,
R. Buckley,
G. deVries,
G. Abelseth,
A. Ni,
R. Gray

From University of Calgary, Alberta, Canada

The incidence of deep-vein thrombosis and the need for thromboprophylaxis following isolated trauma below the knee is uncertain. We have investigated this with a prospective randomised double-blind controlled trial using low molecular weight heparin with saline injection as placebo in patients aged between 18 and 75 years who had sustained an isolated fracture below the knee which required operative fixation. All patients had surgery within 48 hours of injury and were randomised to receive either the placebo or low molecular weight heparin for 14 days, after which they underwent bilateral lower limb venography, interpreted by three independent radiologists. Further follow-up was undertaken at two, six, eight and 12 weeks.

A total of 238 patients fulfilled all the inclusion criteria, with 127 in the low molecular weight heparin group and 111 in the placebo group, all of whom underwent bilateral venography. There was no statistically significant difference in the incidence of deep-vein thrombosis between those patients treated with low molecular weight heparin or the placebo (p = 0.22). The number of deep-vein thromboses in the two groups was 11 (8.7%) and 14 (12.6%), respectively. Age and the type of fracture were significantly associated with the rate of deep-vein thrombosis (p = 0.001 and p = 0.009, respectively) but gender, co-morbidities and the body mass index were not.

The overall incidence of deep-vein thrombosis in this series was 11%. There was no clinical or statistical significant reduction in the incidence of deep-vein thrombosis with the use of thromboprophylaxis. However, we accept that owing to a cessation of funding, recruitment to this trial had to be ended prior to establishing the necessary sample size. Our results cannot, therefore, categorically exclude the possibility that low molecular weight heparin treatment could be beneficial. We recommend a further multicentre trial be undertaken to resolve this matter.

■ D. P. Goel, MD, MSc, FRCSC, Clinical Fellow
■ A. Ni, MSc, Biostatistician
Department of Orthopaedics
University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada.

■ R. Buckley, MD, FRCSC, Orthopaedic Surgeon
Department of Orthopaedics
■ R. Gray, MD, FRCSC, Radiologist
Department of Diagnostic Imaging
Foothills Hospital, 1403 29th Street NW, Calgary, Alberta T2N 2T9, Canada.

■ G. deVries, MD, FRCSC, Orthopaedic Surgeon
1015 Regent Street, Fredericton, New Brunswick E3B 6H5, Canada.

■ G. Abelseth, MD, FRCSC, Orthopaedic Surgeon
Department of Orthopaedic Surgery
Rockyview General Hospital, 7007-14 Street SW, Calgary, Alberta T2V 1P9, Canada.

Correspondence should be sent to Mr R. Buckley; e-mail: buckclin@ucalgary.ca

Deep-vein thrombosis (DVT) is a common medical condition associated with considerable morbidity and mortality. Associated complications include death, post-thrombotic syndrome, right ventricular dysfunction, increased right arterial pressures and the risk of recurrent DVT.[1] Pulmonary embolism (PE) remains the most serious and life-threatening complication of DVT and approximately 10% of symptomatic PE are rapidly fatal. Further, 25% of affected patients are thought to die within one year following a PE and its associated cardiopulmonary complications.[1]

The incidence of DVT has been reported in the literature for a variety of orthopaedic conditions.[2-5] The risk factors are well documented and include pregnancy, hormone replacement therapy, prolonged immobility, obesity, increasing age and long bone trauma.[6-9] The majority of the published work on risk factors and stratification of patients susceptible to DVT has been summarised by Geerts et al[3] and has been recently updated.[10,11] It has helped to establish pathways for the prevention of DVT in both patients and those undergoing elective surgery. The prophylaxis of DVT remains controversial, in particular the type of chemical thromboprophylaxis.[12] Furthermore, variation in guidelines is observed between different countries.[13]

A study by Abelseth et al[14] using venograms found an incidence of 28% of DVT following isolated fractures of the distal lower extremity. These patients did not receive thromboprophylaxis. DVT was higher in those patients with fractures of the tibial plateau. There have only been isolated case reports of DVT/PE following foot surgery, with the overall incidence precluding the need for thromboprophylaxis.[15-17]

Table I. Inclusion and exclusion criteria for subjects eligible for the final analysis

Inclusion criteria	Exclusion criteria[*]
Male and female patients 18 to 75 years of age	Non-surgical treatment
Patients with unilateral displaced, fractures below the knee requiring operation	Fractures above the knee
Patients with simultaneous injury of a minor nature (eg. conservatively managed wrist, scapula, clavicular fracture not inhibiting patient mobilisation)	Polytrauma patients
	Fractures not treated within 48 hours
	Patients with history of DVT or PE
	Patients limited from early mobilisation
	Patients with foot fractures
	Medical contraindications to surgery
	Patients receiving anticoagulation
	Inability to provide consent
	Patients with platelet counts less than 100
	Patients with elevated serum creatinine > 200 μmol/L

* DVT, deep-vein thrombosis; PE, pulmonary embolism

For all other fractures above the foot and below the knee the incidence of DVT has been reported to range from 10% to 40%, with no evidence supporting or refuting the need for prophylaxis. A large randomised controlled trial by Selby et al[16] enrolled 1200 patients and used single limb ultrasound scans following certain fractures of the lower limb. Most of these patients were treated non-operatively (93%), and the majority (60%) of fractures were distal to the ankle. It was concluded that following isolated foot and ankle surgery in healthy patients, thromboprophylaxis was not indicated. Abelseth et al[14] found an overall incidence of 20% to 28% of DVT following fractures distal to the knee, whereas others have observed an incidence ranging from 3% to 40%.[18-20]

Currently, it is unclear whether DVT prophylaxis is indicated post-operatively in patients with these fractures, despite a number of studies which have examined this issue.[2-9,18] We therefore undertook a prospective randomised controlled trial in order to establish a definitive answer. The primary outcome measure was to establish the incidence of DVT in patients with fractures below the knee who had received either a low molecular weight heparin (LMWH), dalteparin (Fragmin, Pharmacia, Pfizer Global Pharmaceuticals, Kirkland, Quebec), or a placebo for two weeks. All had bilateral lower leg venography. Other outcomes included adverse events, compliance with the medication and follow-up. The patient demographics were also described.

Patients and Methods

The study was carried out between December 2000 and July 2006 on patients between the ages of 18 and 75 years admitted with unilateral isolated fractures below the knee which required operative fixation. Patients with minor simultaneous injuries were also included if they were able to mobilise. The criteria for exclusion are summarised in Table I.

Approximately 900 patients were eligible. Patients were excluded for several reasons, including fear of using self-
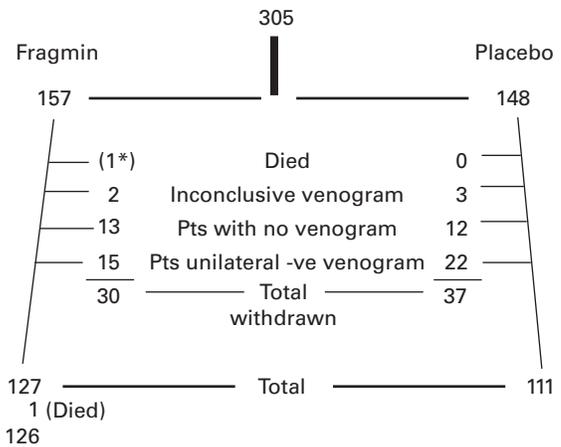
Fig. 1

Consort diagram showing details of withdrawn patients in both groups.

administered syringes at home and if surgery was delayed beyond 48 hours. A total of 305 patients were entered into this study during the period of enrolment which was stopped in 2006 as the sponsor discontinued funding. A total of 37 patients were excluded because of incomplete bilateral venography or the use of ultrasound for investigation. They had either undergone single-limb venography or bilateral ultrasound examination if the venograms were technically difficult to perform. A further 25 patients did not have venograms performed, and five patients refused to be randomised following enrolment in the study and were therefore excluded. Withdrawn patients (67) are listed in the Fragmin and placebo groups (Fig. 1). The final analysis involved 238 patients, of whom 127 were in the Fragmin-treated group and 111 in the placebo group. All had bilateral venography performed at two weeks post-operatively. Although a single patient from the Fragmin group

Table II. Demographic data for all patients

Group	Mean age (range)	Gender (%)	Mean BMI* (range)	Smoker (%)
Placebo (111)	42.1 (19 to 74)	M 67 (*60.3*) F 44 (*39.6*)	26.7 (15 to 44)	38 (*34.2*)
Fragmin (126)	39.8 (20 to 69)	M 80 (*63.4*) F 46 (*36.6*)	27.0 (16 to 46)	29.0 (*23.1*)

* BMI, body mass index

Table III. Distribution of fracture types in both groups and of deep venous thromboses according to fracture type

Group	Tibial plateau	Tibial shaft	Ankle	Pilon	Not recorded
Placebo (111)	17	17	70	6	1
Fragmin (126)	13	22	80	9	2

died several months after the initial two-week follow-up from causes unrelated to thromboembolic disease, the venography result was included in the final data analysis. The majority (182) of the patients were treated and followed up by the senior author (RB), with the remainder treated by surgeons in other hospitals. All patients were followed for a minimum of three months following surgery, or until the fracture had united, and were questioned and examined clinically for symptoms and signs of a DVT. Patient compliance with injections and follow-up was greater than 95% in both groups.

Demographic information is presented in Table II. The overall distribution of the types of fracture was similar in both arms of the study, with those at the ankle representing the majority of injuries in both groups. Higher-energy injuries such as pilon fractures, high-grade fractures of the tibial plateau and complex fractures of the tibial shaft were represented less often, but in similar proportions in both groups (Table III). Post-operatively the median length of stay was three days (1 to 22) in both groups, with no statistically significant difference (p = 0.53) between groups.

Study design. This was a prospective randomised, parallel-group, double-blind, placebo-controlled clinical trial. A statistician and pharmacist at the co-ordinating centre randomised a total of 305 patients via computer generation in a ratio of 1:1 to receive either LMWH or a placebo for 14 days. All patients had the opportunity to review the study with the investigator and/or study nurse before giving informed written consent. Patients in whom it was not possible to obtain a venogram were excluded from the overall analysis but were reported in the study. All the fractures were treated by operation within 48 hours of admission in hospital.

Each group of patients received identical pre-filled syringes containing either Fragmin or saline as the placebo, which was administered by subcutaneous injection in the abdominal wall. Pre-filled syringes were supplied as single-dose injections containing 2500 IU or 5000 IU anti-factor Xa or matching syringes containing placebo.

The treatment schedule was as follows: 2500 IU or matching placebo was administered subcutaneously two hours pre-operatively. This was followed by 2500 IU or matching placebo subcutaneously eight hours post-operatively, and 5000 IU or matching placebo subcutaneously on the following days each morning up to and including the 14th day. Owing to the double-blind nature of the study, all patients received a general anaesthetic for surgical fixation to avoid any potential adverse reaction to spinal anaesthesia in those patients receiving Fragmin. Patients were instructed to self-administer subcutaneous abdominal injections prior to discharge from hospital, when they were provided with sufficient syringes to continue self-administration until the 14th day.

Post-operative rehabilitation was standardised and ward-based physiotherapists directed the patients in early movement exercises. All fractures received a post-operative dressing or immobilisation in a cast, depending on the type of fracture. Clotting studies for evidence of platelet dysfunction were performed twice weekly during the hospital stay, and then repeated on day 14. All patients were reassessed on or about 14 days after operation and bilateral venography was performed. The Fragmin or placebo was discontinued at this point. Further clinical follow-up was scheduled for six weeks and until complete healing of the fracture had occurred. In the event of clinical findings consistent with DVT prior to day 14, a venogram was performed. However, if this was not possible, an ultrasound study was undertaken. A DVT proximal to the knee was managed medically. A negative test did not preclude the patient from continuing the trial.

Complications attributable to anticoagulant therapy, such as bleeding, were determined by the clinical history and physical examination prior to discharge, at the time of venography and at subsequent visits. In order to increase treatment compliance, patients were instructed to return all syringes on day 14, when all concomitant therapy was recorded. Medications enhancing the effect or contributing

to the anticoagulant action of Fragmin were discontinued unless clinically necessary, otherwise the patient was excluded from the study. Other information collected included patient demographics, the type of fracture and the number of DVTs for each type.

Assessments of efficacy. The primary endpoint was the difference in the incidence of DVTs demonstrated by bilateral venography by day 14. All the radiologists were blinded to the study group. Approximately 50 ml of Optiray 320 (Tyco Healthcare, Mallinckrodt Inc., Hazelwood, Missouri) contrast medium was infused into each foot. A tourniquet was applied to the distal lower leg to promote filling of the deep venous system. Image intensification was used to visualise the superficial and deep venous systems of each leg. Assessment of the venous system was considered complete if the femoral vein could be identified proximally. A test was considered positive if an intraluminal defect was observed in two different views. Three senior interventional radiologists reviewed the venograms, with any difference of opinion resolved by consensus. Pulmonary embolism was assessed using a standard protocol and the classification system described elsewhere.[21]

Assessment of safety. All adverse events were monitored and recorded with clinical examination and regular haematological, biochemical and urinary investigations during the routine management of the patients while in hospital. Patients were questioned about adverse events. Problems due to bleeding were classified as major or minor, with major bleeding defined as a fall in haemoglobin of ≥ 2 g/dl within a 24-hour period resulting in transfusion of ≥ 2 units of blood, intracranial, intraspinal, intra-ocular, retroperitoneal or pericardial bleeding, and causing death. Minor bleeding was considered present if overt bleeding was encountered which did not meet the criteria for major bleeding. Following the enrolment of 25% of the total number of patients required for the study, a third-party safety analysis was carried out by a statistician. All statistical parameters were assessed and determined to be safe, enabling the study to continue.

Statistical analysis. A sample size calculation was carried out to assess the number of patients necessary to achieve 80% power. The prevalence of DVT following fractures distal to the knee has been reported to be between 20% and 28% of patients.[14] We adopted 24% as the prevalence used in the sample size calculation. A 10% reduction in the incidence of DVT would be considered significant.[14,22] Using Fisher's exact test, we would require 218 patients in each study arm for a total of 436 patients. An audit of our patients identified that we treated 558 per year with fractures below the knee, and if we had demonstrated a decline of 10% in this group, 55 per year would be influenced and not develop a clot. The demographic variables at entry into the study were summarised for each group. Where these were quite different between the two study groups, their potential confounding effect on the relationship between treatment with Fragmin and the incidence of DVT was

checked by fitting two logistic regression models (model A included only Fragmin as the independent variable; model B included Fragmin and the demographic variable as independent variables) and then comparing the estimated coefficient for Fragmin in the two models. If the difference in the coefficient exceeded 10% of the estimated coefficient in model A, the demographic variable under investigation would be considered as a confounder. Further, we considered that age, gender, body mass index (BMI), and certain medications might be associated with the outcome. This was analysed using a logistic regression model with these factors as independent variables, and reported if their main effect was found to be statistically significant. Given that a typical 'trauma population' has a low rate of compliance and a 10% to 20% drop-out rate, 80% follow-up in this patient population was considered probable. With this prospective design, we also had the opportunity to compare the drop-out rates in 'placebo' with the intervention group to document potential selection bias. If non-compliance arose within our trial during the initial two-week follow-up period when a venogram was essential, it would not be possible to assess the primary outcome measures, as these drop-outs did not receive bilateral venograms. Patients who participated to completion of the trial had an outcome, whereas drop-outs did not. The interventional venography was complete in those who completed the trial, but drop-outs had no venogram and did not have a result recorded. All patients were therefore analysed within the group to which they were randomised, with the exception of those not completing the bilateral venograms. Safety analysis was conducted at an interim interval on advice from our statistician at a very high level of significance (p = 0.001). According to our third-party analysis, there were no safety concerns at 25% of study completion. Our final level of statistical significance was 0.05.

All patients were informed about the study by the surgical team and gave written informed consent. The local Institutional Review Board and Independent Ethics Committee approved the study, which was performed in accordance with the Helsinki Convention.

Results
The data are presented in accordance with the guidelines established for randomised controlled trials in the CONSORT statement.[23] All patients entered/enrolled in this trial are accounted for in Figure 1.

A total of 476 venograms were performed on the 238 patients in the study, which identified 14 DVTs (12.6%) in 111 patients in the placebo group and 11 DVTs (8.7%) in 127 patients in the Fragmin group (Table IV), all distal to the knee. A comparison of the incidence of DVT between the two groups found no statistically significant difference (Fisher's exact test, p = 0.22). The 95% confidence interval for the difference in rate of DVT formation between the groups was -11.78% to 4.02%, which includes a pre-determined clinically significant difference of 10%. In

Table IV. Number of deep venous thromboses (DVT) per Fragmin and placebo group

		DVT	
	Total number	Number	Rate (95% CI)*
Placebo	111	14	12.6 (6.44 to 18.79)
Fragmin	126	11	8.73 (3.80 to 13.66)

* 95% CI, 95% confidence interval

six patients a DVT was detected in the contralateral, uninjured leg (four in the placebo group and two in the Fragmin group). All patients with a DVT were asymptomatic and did not require medical management. There was no proximal extension of the thrombus. A total of five venograms were inconclusive, despite an attempt by the radiologists to obtain a consensus. These patients were excluded from the final data analysis and were not treated for DVT.

Risk factors. Several factors were assessed for their own effect on the development of a DVT, regardless of the use of Fragmin, using univariate logistic regression. These factors include age, BMI, gender, smoking status, fracture energy, fracture type, and 11 significant medical issues. These comprised otherwise good health, or the presence of the following conditions: carcinoma, obesity, venous insufficiency, diabetes, peripheral vascular disease, renal disease, bowel disease, blood disorders, smoking, prior leg injury and the use of oral contraceptive. In addition we examined the influence of the type of immobilisation, whether casting, splinting or the use of a light dressing, as a risk factor of developing a DVT. Multivariate logistic regression showed no statistically significant difference for the methods employed. The age and type of fracture were the only two variables which were found to be significantly associated with the presence of a DVT (univariate analysis, p = 0.001 and p = 0.009, respectively). These two variables, together with Fragmin, were further analysed with a multivariate logistic regression model with DVT rate as the dependent variable. This revealed that age and the type of fracture are two risk factors for development of DVT in both Fragmin- and placebo-treated patients, but multivariate logistic regression also showed no statistically significant increase in DVT in patients who suffered higher-energy fractures, compared to those patients with low-energy injuries (p = 0.26). The mean age and the proportion of smokers was examined for evidence of a confounding effect in the relationship between Fragmin treatment and DVT incidence rate using the two logistic regression models described previously. Neither age nor smoking status was considered a confounder. Given the overall number of fractures, it is difficult to define a specific type as increasing the risk for DVT, but those of the tibial plateau did display a tendency towards higher rates of DVT in our study (Table III).

Secondary outcomes. There was one death among the patients treated with Fragmin due to causes unrelated to

thrombosis or its sequelae. There were no major or minor bleeding complications or cases of heparin-induced thrombocytopenia. We had 96% follow-up and 97.5% drug compliance within our study population using diaries and an agreement with patients to return empty syringes.

Discussion
Deep-vein thrombosis is a common problem in surgery for trauma, and its management presents a dilemma. The incidence of DVT following isolated fractures below the knee and the indications for thromboprophylaxis are unknown. We attempted to resolve this deficiency with our prospective randomised study. The venogram has been verified as the benchmark for detecting DVT.[24-28] However, some feel that ultrasound is now becoming equal in diagnostic sensitivity, with less associated risk.[29,30] Ultrasound is non-invasive and less expensive than venography but it is less able to detect a DVT proximal to the popliteal area, from where the risk of pulmonary embolus is considerably greater.[4] Furthermore, difficulties associated with the use of ultrasound include reduced rates of detection in swollen limbs, poor identification around the knee, and unrecognised duplication of the superficial femoral vein, effectively underestimating the overall incidence of DVT.[31,32] In Asian populations, where DVT is rare, a higher incidence of DVTs has been found following venography than after duplex ultrasonography.[33] Measurement of the D-dimer level to justify further investigation for DVT has been advocated by some, but recent literature has shown normal D-dimer values in up to 30% of patients with DVT distal to the knee and in 5% proximal to it.[34] Although a sensitivity of 96% exists for elevated D-dimer levels in the presence of proximal DVT, it is inconsistent in predicting the presence of DVTs requiring medical management.[34] At the start of our trial a venogram was considered the best method for detecting DVT.[35-37] Although there have been several studies challenging venography with other non-invasive methods of imaging, we believe venography continues to be the appropriate choice for both symptomatic and asymptomatic DVT, with the highest specificity and sensitivity.[32]

A large descriptive study by Knudson et al[19] observed findings with regard to age. Although not statistically significant, in our study, age over 40 and the type of fracture are risk factors for the development of post-operative DVT regardless of thromboprophylaxis.[19] This was observed using a multivariate analysis, yet statistically it was not sig-

nificant. Several other risk factors for DVT have been identified.[38] DVT in the uninjured leg has not been reported in the literature except in the previous incidence study by Abelseth et al.[14] We believe that the incidence of DVT is theoretically under-reported with unilateral examination. This study reports an increase in the number of DVTs in the contralateral uninjured leg in patients treated with placebo compared with Fragmin. Although there are not enough patients to define this entity conclusively, it is clear that further analysis of the uninjured limb may be worthwhile. Although most isolated DVTs below the knee are not treated medically, a post-thrombotic syndrome may provide long-term morbidity, mandating further investigation.[39] The management of this entity is described in detail in new Antithrombotic guidelines.[10]

We found no statistically significant difference in the incidence of DVT according to the type of post-operative immobilisation. This contrasts with the findings of Kock et al,[40] who observed a 3.9% incidence of DVT in patients treated with plaster immobilisation who received thromboprophylaxis. Immobilisation alone appears to be an independent risk factor for DVT in fractures of the ankle.[41] There are probably a number of confounding factors when considering the influence of immobilisation, the most significant being the time to mobilisation. Historically, the length of hospital stay was much higher for similar fractures and may explain the increased risk of DVT in patients immobilised with a plaster cast in an older report.[14] In our series all patients were operated on within 48 hours and mobilised promptly by a physiotherapist, potentially reducing the risk associated with specific types of post-operative immobilisation.

The BMI has been reported by some to be a risk factor for the onset of DVT.[3,7,42] This might be considered to result from increased venous stasis in patients with a larger BMI, who possibly mobilise more slowly. However, we were unable to confirm this in our study, which was consistent with other reports,[43,44] but the range of BMI in our study dictates that caution be exercised when extrapolating to patients with a higher BMI.

Overall, the detection of DVT in both groups was low (12.6% placebo and 8.7% Fragmin) and the difference was not statistically significant (p = 0.22). The incidence of DVT in this study as a whole was 11%. Because of the withdrawal of funding we were unable to recruit sufficient numbers of patients to satisfy our calculation of sample size. The difference in confidence intervals between groups suggests that the failure to reach statistical significance was an inconclusive result due to small sample size rather than a negative result, with the possibility that statistical significance might have been attained with a larger sample.

We did not encounter any bleeding complications due to the use of Fragmin and there was no alteration in the platelet count. We understand that heparin-induced thrombocytopenia following the use of LMWH has been reported only in isolated cases.[45]

The compliance with our two-week protocol was good and reflected that found in groups treated for more than six weeks.[46]

The surgical risk factors for DVT are well documented in the literature for joint replacement, polytrauma and certain fractures, but evidence supporting the use of thromboprophylaxis for fractures below the knee is limited. Given the wide variation in the incidence of DVT and types of prophylaxis in these patients, a prospective randomised controlled trial was indicated. The overall incidence of DVT in our patients was 11%. This included those found to have a DVT in the contralateral uninjured leg. None of the DVTs detected extended above the knee. There was no statistically significant difference in the incidence of DVT in patients receiving Fragmin or those having the placebo. Our study was underpowered to state categorically that the Fragmin did not contribute to a reduction in the rate of DVT. We feel that larger multicentre studies will be needed to answer the specific questions about the incidence and risk factors for DVT in these patients.

Supplementary material

A further opinion by Mr D. Warwick is available with the electronic version of this article on our website at www.jbjs.org.uk

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