A single-centre prospective study of clinical and haemostatic risk factors for venous thromboembolism following lower limb arthroplasty

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Summary

Previous studies report conflicting results concerning the potential significance of thrombophilic genotypes in postarthroplasty venous thromboembolism (VTE). This study assessed thrombophilic genotypes, haemostatic and clinical variables as independent risk factors for VTE postarthroplasty. A total number of 569 patients undergoing elective lower limb arthroplasty at a single centre were prospectively studied. All patients were interviewed and had blood samples collected preoperatively. Bilateral lower limb ultrasonography was performed at day 7 ± 2 postoperatively in all patients (ventilation/perfusion lung scanning in symptomatic patients only). The incidence of inhospital postoperative VTE was 26%. In univariate analysis – increased age, knee arthroplasty, recent surgery, general anaesthesia, shorter operation time, non-receipt of blood transfusion and differences in surgical practice (including use of pneumatic calf compression, surgical drains and postoperative bandaging techniques) were significantly associated with VTE. Factor V Leiden, prothrombin G20210A and MTHFR C677T mutations were not significant risk factors for VTE, and of all haemostatic variables tested, only median activated partial thromboplastin time showed significant difference between VTE and non-VTE patients (34 s vs. 33 s). Multiple logistic regression analysis demonstrated that increased age, knee arthroplasty and individual surgeon's routine practices were the only significant independent risks for VTE; hence routine preoperative blood screening for a potential hypercoaguable state is not indicated in this surgical setting.

Keywords: thrombophilia, clinical risk factors, venous thromboembolism, arthroplasty.

Patients undergoing lower limb arthroplasty have the highest incidence of venous thromboembolism (VTE) amongst any surgical patient group. Even with extended prophylaxis and novel antithrombotic agents (including fondaparinux and ximelagatran), deep venous thrombosis (DVT) can still occur in a significant number of arthroplasty patients (Bauer *et al*, 2001; Cohen *et al*, 2001; Eikelboom *et al*, 2001; Hull *et al*, 2001; Turpie *et al*, 2001; Colwell *et al*, 2003; Eriksson *et al*, 2003). Clinical factors that may increase VTE risk in these patients are well documented and easily identified, however the potential role of haemostatic variables is less clear, with a limited number of large studies.

In several previous studies, the thrombophilic genotypes factor V Leiden/activated protein C (APC) resistance and prothrombin G20210A have all been reported to be a significant risk factor for postarthroplasty DVT (Lindahl *et al*, 1999; Lowe *et al*, 1999). However, other groups have failed to demonstrate such an association (Philipp *et al*, 1998; Ryan *et al*, 1998). Results from a large multicentre trial also found that neither factor V Leiden nor prothrombin G20210A were found to be risks for DVT following total knee or hip arthroplasty, although prothrombin G20210A appeared to be associated with symptomatic DVT (Wahlander *et al*, 2002). Thus, the published data concerning these genotypes appears

to be somewhat conflicting. There is limited data concerning the methylene tetrahydrofolate reductase C677T (MTHFR C677T) mutation, with one small case–control study reporting no evidence of an association between MTHFR C677T genotype and thrombosis in 85 patients undergoing elective total hip arthroplasty (Philipp *et al*, 1998). A large, comprehensive multicentre study examined 29 preoperative haemostatic variables in patients undergoing elective hip surgery (Lowe *et al*, 1999). Although it was demonstrated that the activated partial thromboplastin time (APTT) and APC sensitivity ratio were significantly lower; thrombin–antithrombin complex (TAT), prothrombin fragments F1+2, d-dimer and factor VIII (FVIII) levels were significantly higher in patients who developed postoperative DVT; these associations were statistically insignificant after multivariate analysis adjustment for clinical factors, with the exception of APTT and APC sensitivity ratio.

One potential reason for disparate results from previous reports may be that some studies contained too few subjects and were therefore insufficiently powered. Moreover, in collaborative trials, differences in surgeons, surgical techniques and DVT prophylaxis may have been confounding variables. To overcome these potential limitations, we designed a clinical trial with sufficient statistical sample size that involved only two orthopaedic surgeons at a single centre.

Subjects and methods

Study population

Consecutive patients undergoing primary elective total hip or total knee arthroplasty at our institution (St Vincent's Private Hospital) under the care of the two participating orthopaedic surgeons were recruited into the study. There were no specific exclusion criteria apart from patients undergoing consecutive bilateral procedures. Written informed consent was obtained from all patients and the study approved by the Campus Research Ethics Committee. All patients were interviewed and relevant demographic and medical history details recorded. Blood sampling for specific genetic and haemostatic testing was performed at the time of routine preoperative blood collection. Buffy coat specimens collected for DNA testing were stored at −80°C. Platelet-poor citrated plasma for haemostatic testing was frozen at −80°C for up to 3 months before testing, except APTT which was performed immediately. Blood sampling for homocysteine testing was performed on the first postoperative day following an overnight fast and EDTA plasma samples were frozen at −80°C. All patients received routine postoperative thromboprophylaxis with enoxaparin (40 mg once daily) and compression stockings during their period of hospitalization. There were differences between the individual surgeon's practices, which included: routine use of intermittent pneumatic calf compression, use of surgical drain, extent of compression bandaging, and mobilization and physiotherapy schedules postoperatively. Bilateral lower limb compression duplex ultrasonography was performed in all patients at day 7 ± 2 postoperatively in a specialized vascular laboratory and reported by a specialist vascular physician. Proximal DVT was defined as thrombosis involving the popliteal vein or above. Testing for pulmonary embolism was performed only if there were suggestive clinical symptoms. Follow-up at 3 months was performed and any new or recurrent episodes of symptomatic VTE recorded.

Laboratory methods

DNA was extracted from peripheral blood buffy coat samples for genetic thrombophilia testing. Factor V Leiden and prothrombin G20210A gene mutations were detected using a multiplex polymerase chain reaction (PCR)-mediated site-directed mutagenesis method that creates a TaqI endonuclease cleavage site, as previously described by (Ripoll *et al*, 1997). MTHFR C677T gene mutation was detected by PCR amplification of genomic DNA and digestion with HinfI (Frosst *et al*, 1995). Plasma homocysteine levels were measured in 145 patients, using the Abbott Homocysteine kit (Abbott Park, IL, USA) on the AxSYM™ immunoassay. Haemostasis tests were performed on the Stago STA analyzer (Diagnostica Stago, Asnieres, France); APTT with Auto APTT (bioMèrieux, Durham, NC, USA); kaolin clotting time (KCT) with Kaoclot (Gradipore, Sydney, NSW, Australia); fibrinogen with thrombin Reagent (Dade Behring, Marburg, Germany); FVIII with Dade Behring deficient plasma; and APC resistance, with results expressed as normalized ratios with coatest APC™ Resistance (Chromagenix-IL, Milan, Italy). TAT and F1+2 were measured by enzyme-linked immunosorbent assay using Enzygnost TAT micro and F1+2 micro kits (Dade Behring) respectively. Haemostatic tests were not performed on the whole group (because of insufficient blood sampling); APTT, KCT and APC resistance on 480 patients and FVIII, TAT and F1+2 on 280 patients only.

Statistical design and analysis

Statistical analysis was performed using ANALYSE-IT for Microsoft EXCEL and SIGMA STAT software (SPSS Inc's, Chicago, IL, USA); chi-square to determine differences between observed proportions, unpaired *t*-test and non-parametric tests to assess significant differences between subgroups and multiple logistic regression analysis to determine the significance of individual risk factors in a multivariate model.

Results

General patient characteristics

A total number of 569 patients were recruited into the study between 1999 and 2003, and their general characteristics are listed in Table I. The overall incidence of inhospital postoperative VTE was 26% (mainly distal DVT), and <10% events were symptomatic. Thrombophilic genotypes were found in 93

Table I. General patient characteristics

Characteristic ($n = 569$)	n (%)
Age	
Median (range)	67 years (20–90 years)
Sex	
Female	291 (51·1)
Male	278 (48·9)
BMI	
Median (interquartile range)	27 (24–30)
Type of joint arthroplasty	
Hip	342 (60·1)
Knee	227 (39·9)
Surgeon (A)	
Hip arthroplasty	290
Knee arthroplasty	154
Surgeon (B)	
Hip arthroplasty	53
Knee arthroplasty	72
Main indication for surgery	
Osteoarthritis	472 (83·0)
Avascular necrosis	37 (6·5)
Other/indication not given	60 (10·5)
Type of anaesthetic	
General	280 (49·2)
Incidence of VTE	
Overall	149 (26·2)
Type of VTE	
Distal DVT	124 (83·2)
Proximal DVT	22 (14·8)
PE	3 (2·0)
Thrombophilia genotype	
Heterozygous factor V Leiden	26 (4·6)
Heterozygous prothrombin G20210A	12 (2·1)
Homozygous MTHFR C677T	59 (10·4)

Table II. Characteristics of patients according to site of joint arthroplasty

Characteristic	Hip ($n = 342$)	Knee ($n = 227$)	P-value
Age			
Median	64 years	71 years	<0·0001
Sex			
Female	169 (49·4)	121 (53·3)	ns
Male	173 (50·6)	106 (46·7)	ns
BMI			
Median	26	28	0·0002
Incidence of VTE			
Overall	30 (8·8)	119 (52·4)	<0·0001
Type of VTE			
Distal DVT	18 (60)	106 (89·1)	
Proximal DVT	11 (36·7)	11 (9·2)	0·0004
PE	1 (3·3)	2 (1·7)	

Values in parentheses are expressed in percentage.
ns, Not significant.

Univariate analysis of all clinical variables

A number of other clinical variables were recorded for each patient. The level of significance for each factor as a potential risk for postoperative VTE was tested in a univariate model and is given in Table IV. Increased age and undergoing a total knee arthroplasty (as compared with hip arthroplasty) were found to be highly significant risks for VTE ($P < 0.0001$). Patients who had undergone recent surgery in the 3 months preceding their arthroplasty had a higher risk of VTE ($P = 0.002$), as did patients who received general anaesthesia ($P = 0.013$). We found that body mass index (BMI) >30, a previous history of cancer or VTE, positive family history of VTE and a poor level of pre-operative physical activity were not significant risk factors in a univariate model. Interestingly, the median duration of operation time was significantly shorter in the VTE group (146 min) compared with the non-VTE group (160 min, $P < 0.0005$); and patients who administered blood transfusion were less likely to have VTE (18%) compared with those who did not receive a blood transfusion (39%, $P < 0.0005$). There was also a significant difference in the overall rate of VTE when individual surgical practices were compared (43·2% compared with 21·4%, $P < 0.0005$).

Multiple logistic regression analysis

The effects of independent clinical and genetic variables on the incidence of DVT were tested using a backward stepwise multiple logistic regression. In this multivariate analysis, only increased age ($P = 0.02$), total knee arthroplasty ($P < 0.005$) and differences in individual surgical routine practices ($P = 0.006$) were significant independent risk factors for postoperative VTE. (Note that the difference in VTE rates found between individual surgical practices was independent of the number and type of arthroplasty performed by each surgeon.)

patients – 4·6% patients were heterozygous for factor V Leiden; 2·1% were heterozygous for prothrombin G20210A and 10·4% were homozygous MTHFRC677T.

Knee arthroplasty compared with arthroplasty

There were some differences in patient characteristics according to site of joint arthroplasty (Table II). Although patients undergoing knee replacement were more likely to suffer with VTE, proximal DVT accounted for only 9% these events (compared with 37% of VTE events in patients undergoing total hip arthroplasty).

VTE patients compared with non-VTE patients

The differences between the VTE and the non-VTE group are listed in Table III. VTE patients were significantly older, however there was no significant difference in prevalence of thrombophilic genotypes. The APTT was the only haemostatic parameter that differed between VTE and non-VTE patients.

Table III. Characteristics of VTE patients compared with non-VTE patients

Characteristic	VTE (n = 149)*	No VTE (n = 420)*	P-value
Age (years)			
Median	72	66	<0·0001
Sex			
Female	74 (49·7%)	217 (51·7%)	ns
Male	75 (50·3%)	203 (48·3%)	ns
BMI			
Median	28	26	0·05
Joint			
Knee	119 (81·0%)	107 (25·5%)	<0·0001
Genotype			
Hetero factor V Leiden	8 (5·4%)	18 (4·3%)	ns
Hetero prothrombin G20210A	4 (2·7%)	8 (1·9%)	ns
Homo MTHFR C677T	14 (9·4%)	45 (10·7%)	ns
Homocysteine (μmol/l)			
Median (interquartile range)	6·4 (5·1–8·6)	6·8 (5·3–9·5)	ns
APTT (s)			
Median (interquartile range)	34 (32–37)	33 (31–35)	0·011
KCT (s)			
Median (interquartile range)	79 (71–92)	78 (69–91)	ns
Fibrinogen (g/l)			
Median (interquartile range)	3·42 (3·08–3·93)	3·46 (3·03–3·94)	ns
APC resistance ratio			
Mean (±2 SD)	0·92 (±0·12)	0·92 (0·13)	ns
Factor VIII (%)			
Mean (±2 SD)	144 (±0·43)	144 (±38)	ns
Fragment 1 + 2 (nmol/l)			
Median (interquartile range)	1·02 (0·83–1·27)	0·92 (0·70–1·29)	ns
TAT complex (μg/l)			
Median interquartile range)	2·34 (1·78–3·25)	2·08 (1·69–2·93)	ns

ns, Not significant.

*Numbers refer to total patient cohort. Haemostatic parameters were not performed in all 569 patients (see text).

A 3-month follow-up

A 3-month follow-up data was available for 538 patients (94·6% total cohort). A total of 10 patients (1·9%) had recurrence, extension, or a new VTE, which included two cases of PE.

Discussion

We performed this study to assess whether clinical risk factors and haemostatic variables could potentially identify those patients who may benefit from more 'aggressive' anti-coagulant prophlyaxis.

Table IV. Univariate analysis of clinical variables as risk factors for postarthroplasty VTE

Clinical variable	P-value
Age (continuous)	<0·0001
Total knee arthroplasty	<0·0001
Recent surgery	0·002
BMI>30	0·849
History of cancer	0·980
Previous VTE	0·122
Family history VTE	0·270
No preoperative physical activity	0·934
General anaesthesia	0·013
Shorter duration of operation time	<0·0005
Non-use of blood transfusion	<0·0005
Individual surgeon's routine practices (includes routine use of pneumatic calf compression, use of surgical drain, extent of compression bandaging, and mobilization and physiotherapy schedules postoperatively)	<0·0005

The overall incidence of inhospital postoperative VTE was 26%, which is within the range reported by other studies (Ryan *et al*, 1998; Lowe *et al*, 1999). Although there has been criticism regarding the use of ultrasound for detection of asymptomatic DVT, we considered its potential advantages, which included a non-invasive method, performance in a specialized vascular laboratory and reduced cost. In previous work performed by the same vascular laboratory, acute DVT was found in 68 of 280 patients (24·3%) undergoing limb arthroplasty; and at 3-month follow-up, only three patients with a 'normal' ultrasound result developed subsequent thrombophlebitis or VTE (Tay & McGrath, 1999). Indeed, a recent review recommends that compression ultrasonography is a valid screening method, provided that specific methodological details are observed (Leizorovicz *et al*, 2003).

The majority of DVT in our study were asymptomatic. Although the clinical importance of asymptomatic DVT is somewhat controversial, we chose to treat all patients with DVT because of the possibility of thrombus extension or propagation. Indeed, a previous study of over 1200 patients undergoing knee arthroplasty found that those with calf thrombi (diagnosed by routine venogram and not based on presence of symptoms) had a significantly increased risk for both asymptomatic and symptomatic PE (Haas *et al*, 1992). More recently, it has also been shown that acutely ill-hospitalized patients with asymptomatic proximal DVT have a significantly increased mortality rate compared with those without thrombosis, and there was also a numerical increase in mortality among patients with asymptomatic distal DVT (Vaitkus *et al*, 2005).

Considering clinical variables initially, we found that patients undergoing knee arthroplasty were more likely to develop VTE, which is consistent with previous reports (Geerts *et al*, 2001). Most were distal DVT, and this probably relates to

local tissue trauma at the site of surgery, use of tourniquet with subsequent distal venous stasis, and manipulation of the knee during surgery.

Patients who developed VTE were significantly older, more likely to have undergone recent surgery or received general anaesthesia – all considered thrombotic risks. Although the median BMI was higher in VTE patients, a BMI >30 was not found to be a significant risk factor. This contrasts with previous studies, which have shown that clinical obesity and increased BMI is a VTE risk in arthroplasty patients (Lowe et al, 1999; Mantilla et al, 2003). Possible reasons for this discrepancy may include differences in study populations and prophylactic measures.

We found that neither a history of cancer nor previous VTE were significant risk factors in this group of patients, which suggests that the arthroplasty procedure itself is more thrombogenic than these factors.

Although the median duration of operation time was significantly shorter in VTE patients, this relates to the fact that knee arthroplasty procedures were significantly shorter than hip procedures. Patients who did not receive a blood transfusion (generally autologous) postoperatively were more likely to develop a VTE. Others have also reported that preoperative donation of autologous blood is associated with a significant reduction in DVT (Anders et al, 1996), which probably results from the favourable reduction in blood viscosity.

A significant difference in VTE incidence was noted between the two surgeons' groups (43·2% vs. 21·4%), which on multivariate analysis testing, could not be attributed to differences in either the number or type of arthroplasty performed by each surgeon. A number of possible contributory factors have been identified, including routine use of pneumatic calf compression, postoperative bandaging techniques, use of surgical drains and postoperative physiotherapy and mobilizing protocols. Pneumatic calf compression is an effective component of VTE prophylaxis in this group of patients. It induces venous turbulence, releases endothelial derived relaxing factor and stimulates fibrinolysis (Bottner & Sculco, 2001). We also need to consider that other management issues may have contributed to this difference in VTE incidence and conclude that this study prompts further investigation of these issues.

We found no significant difference in the frequencies of any of the thrombophilic genotypes in VTE compared with non-VTE patients. This is consistent with findings from a multicentre trial of 1600 patients undergoing lower limb arthroplasty, which examined factor V Leiden and prothrombin G20210A mutations (Wahlander et al, 2002). While other smaller studies also support these findings (Philipp et al, 1998; Ryan et al, 1998), some groups have demonstrated that APC resistance/factor V Leiden is a significant risk factor for postarthroplasty DVT (Lindahl et al, 1999; Lowe et al, 1999). In our study, APC resistance was not found to be a significant risk factor for VTE. We also demonstrated no significant

association between any of the haemostatic parameters tested and postarthroplasty VTE, except for APTT, which was slightly longer in VTE patients (univariate analysis only). This finding contrasts with that of a multicentre study (Lowe et al, 1999), which reported that APTT measured by the local laboratory was in fact shorter (using multivariate analysis) in those who developed DVT by 4%. However, the difference (c. 1·6 s) was not large enough to be of clinical utility in predicting DVT. Potential reasons for disparate results between different studies includes too small a sample size in some studies, involvement of multiple hospitals, differences in surgeons and surgical techniques as well as differences in DVT prophylaxis regimes.

In summary, the observations made in this study demonstrate that clinical variables, such as increased age, undergoing a knee arthroplasty and differences in surgical practices (which include routine use of pneumatic calf compression), are the only significant risk factors for DVT postarthroplasty. Hence, preoperative screening patients for thrombophilic genotypes and haemostatic risk factors in an attempt to identify a particularly high-risk group is not recommended. Whether patients with a higher VTE risk clinical profile should receive more aggressive anti-coagulation was not addressed in this study, and it would be interesting to stratify patients in future trials of new anti-coagulants according to their level of clinical risk.

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