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Very Low Dose Warfarin as Prophylaxis Against Ultrasound Detected Deep Vein Thrombosis Following Primary Hip Replacement

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One mg daily warfarin was compared to variable dose warfarin (PT 1.3–1.5 times the normal PT), as prophylaxis against deep vein thrombosis (DVT) following unilateral hip replacement for degenerative joint disease (DJD). Ninety-eight patients entered onto study after having had negative color Doppler ultrasounds of the legs. Patients receiving 1 mg began therapy 7 days preoperatively and continued daily until discharge. Patients receiving the variable dose took 5 mg the night preoperatively, and thereafter daily based upon the daily PT. Seventy-eight patients completed the study protocol. No patient completing the protocol had DVT or pulmonary embolus (PE). Based upon intent to treat for all registered patients, one from each group had DVT after withdrawal from study. For patients receiving 1 mg warfarin daily, PTs extended none or slightly. Therefore, 1 mg warfarin can be used to prevent postoperative DVT following elective hip surgery. Am. J. Hematol. 71:69–74, 2002. © 2002 Wiley-Liss, Inc.

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INTRODUCTION

The ideal method for preventing post-operative DVT of the legs would be antithrombotic regimen that would not be an anticoagulant, would be 100% effective, would be inexpensive, would be easy to administer, and would require no laboratory surveillance. The commonly applied approaches now in use, including low-dose heparin, low molecular weight heparin, variable dose warfarin, and pneumatic compression stockings, do not meet the criteria for the ideal.

A technique that would approach the ideal would be to use very low dose warfarin at doses that would not prolong the PT but which would be antithrombotic. The applicable concept would be to maintain a homeostatic balance of coagulation, dampening the stresses leading to excessive coagulation but without loss of surgical hemostasis.

We have reported previously the results of using this approach among patients requiring central venous catheters for hyperalimentation or chemotherapy [1–3]. Patients requiring central venous catheters for chemotherapy were randomly assigned to receive either no anticoagulant or 1 mg of warfarin daily, beginning 3 days before the catheter was inserted. The warfarin-treated group had a significant reduced incidence of venogram-documented subclavian vein thrombosis surrounding their catheters during the 90-day observation period (9.2% vs. 42%) [3]. This has been confirmed by other investigators [4].

Based upon those results, we elected to study very low dose warfarin to prevent DVT in patients undergoing

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total hip replacement for DJD. We studied the effectiveness of giving 1 mg of warfarin daily, beginning 1 week before surgery, and compared the outcome to our routine prophylactic regimen of variable-dose warfarin, with the first dose of 5 mg given the night before surgery. If the 1 mg of fixed-dose warfarin regimen was found to be as or more effective as the variable dose regimen, then the very low dose regimen would approach the ideal by offering efficacy with increased ease of use, at less risk and less cost.

MATERIALS AND METHODS

Patients scheduled for elective total hip arthroplasty for DJD were candidates for this study if they had no personal or family history of venous thrombotic or hemorrhagic diseases; had normal platelet count, bleeding, prothrombin, and partial thromboplastin times; and had normal renal and liver functions. All patients were referred to this center without regard for either ethnic or racial background. Patients with established need for anticoagulation for atrial fibrillation or for vascular diseases were excluded from study, as were those with any known hypercoagulation syndrome.

Baseline color Doppler duplex ultrasound images, with compression technique, were obtained of both lower extremities before randomization. Patients with no evidence of venous thrombosis were then randomized. The ultrasounds were repeated at the time of discharge or after 7 days postoperatively, after 6 weeks postoperatively, or at time of clinical suspicion of DVT or PE. Any abnormal ultrasound was followed by venogram. Clinical suspicion of pulmonary embolus was evaluated by ventilation/perfusion lung scan and, if necessary, a pulmonary arteriogram. The two technicians and one radiologist who performed all studies were blinded to the patients' status on study.

Informed consent was obtained according to the hospital's Institutional Review Board.

Patients were randomized either to receive 1 mg daily, to begin 7 days prior to surgery and to be continued daily throughout hospitalization (Group 1), or to receive variable-dose warfarin, receiving 5 mg the night prior to surgery, followed by daily variable doses to maintain PT at 1.3–1.5 times normal throughout the hospitalization (Group 2). Warfarin therapy after discharge was at the discretion of the surgeon, but all patients remained on their respective therapies until their follow-up visit. All patients wore elastic stockings. Pneumatic compression stockings were not allowed in this study.

The anesthesia technique and the use of intraoperative plasma volume expanders, including low molecular weight dextran (LMWD), were at the discretion of the surgeons and anesthesiologists.

The estimated volume of blood loss during surgery and transfusion requirements was recorded. Bedside exams were conducted daily to detect hemorrhage, DVT, PE, or warfarin-induced skin necrosis. Prothrombin times and complete blood cell counts were measured on day of surgery and then usually daily until day of discharge using routine laboratory procedures.

TABLE I. Results of Randomization

	Very low dose	Variable dose
Total no. of patients	49	49
Males/females	30/19	25/24
Median age (years)	66	66
Range of ages (years)	29–84	31–91
Mean age (years)	65.3	61.9
Received LMWD	29	23

The study endpoints were venogram-proven DVT, lung scan- or angiogram-proven PE, or negative Doppler ultrasound exams at discharge and after 6 weeks follow-up.

The study was powered to detect a 15% difference after 90 patients if a difference did exist. If no difference emerged, then the study was to be closed, and the hypothesis would be accepted that the two prophylactic regimens were equal. Student's *t*-test was used to detect defects in randomization of study populations and results. All analyses were based upon intention to treat after randomization.

RESULTS

Ninety-eight patients were registered on the study, with 55 males and 43 females. The median age was 65 years of age (range: 29–91 years of age). All but 3 cases were operated upon by teams led by one senior surgeon (B.B.). Forty-nine patients were randomized to Group 1 and 49 to Group 2 (see Table I).

Twenty patients were withdrawn from analysis due to protocol violations: 14 from Group 1, and 6 from Group 2 (see Table II). No patient who completed either arm of the protocol had DVT or PE at discharge or at the 6-week follow-up exam. It was apparent that no difference between the groups emerged, and the study was closed.

Based upon intention to treat, but withdrawn from study due to protocol violations, one patient from each group had DVT. The one patient withdrawn from Group 1, who developed DVT on day 4 postoperatively, had not taken all 7 days of the preadmission warfarin, plus while in hospital, he had received by error variable-dose warfarin. In addition, he also took dexfenfluramine (Redux®) without the knowledge of the investigators until the day of admission. The patient who was withdrawn from Group 2 had DVT at the follow-up exam 6 weeks after discharge; this patient had been withdrawn because he had been randomized to receive variable-dose warfarin

TABLE II. Protocol Violations: 20 Patients Withdrawn

	Very low dose (group 1)	Variable dose (group 2)
Nonsteroidal anti-inflammatory drugs	8	3
Pneumatic compression stockings	1	
Drug-induced thrombocytopenia		1
Atrial fibrillation; heparin given	1	
Dose errors:		
Did not take preoperative warfarin	1	
Received 1 mg daily after 5 mg pre-op		1
Received 1 mg daily; none 7 days pre-op		1
Variable dose 1 day	2	
Variable dose 2 days	1	

TABLE III. Estimated Blood Loss (mL)[a]

	Mean	Median	Range
Very low dose	557	500	200–1,400
Variable dose	625	500	200–2,250

[a]Based upon intention to treat.

TABLE IV. Transfusions Given (units of blood)[a]

	Mean	Median	Range
Very low dose warfarin	2.3	2	0–5
Variable-dose warfarin	2.4	2	0–5

[a]Based upon intention to treat.

but erroneously received fixed, very low dose warfarin without having had the 7 days of warfarin preadmission. Neither patient received LMWD, and both had general anesthesia.

The estimated blood loss at the time of surgery and the transfusion requirements were the same for both groups (see Tables III and IV).

The maximum PT values for each patient in both study groups are shown in Figure 1. Median PT for those in Group 1 was 13.8 sec, and the median PT for those in Group 2 was 17.3 sec ($P < 0.05$).

The study had been powered to detect a significant difference of 15% after 90 patients. However, as no difference emerged, the study was closed, and the null hypothesis was accepted.

DISCUSSION

The efficiency of prophylactic anticoagulation is traditionally measured against the risk of iatrogenically induced hemorrhage. The method being reported here appears to maintain an antithrombotic potential but with either nil or minimal additional risk of hemorrhage.

This study was to extend our finding that very low fixed-dose warfarin was prophylactic against DVT in settings other than those already reported [1–5]. For this we chose to study patients receiving primary hip replacement for degenerative joint disease. Conclusions drawn from this study should not be applied to patients at even higher risk for DVT, such as those with traumatic fractures, pathologic fractures, metastatic adenocarcinomas, septic joints, joint revisions, prior history of DVT, concomitant pregnancy, or family history of thrombophilia, such as lupus anticoagulant, activated protein C resistance, etc. These high-risk groups require separate prospective studies.

This study used as the comparative arm the therapy that had been the standard of practice in our hospital. With this construct, we hoped to demonstrate that fixed low-dose warfarin was equal to variable-dose warfarin in preventing DVT. If true, the fixed very low dose regimen would displace the variable-dose regimen for these selected patients, since it would be easier, less expensive, and less risky to use.

This study was designed to take advantage of consistency of surgical approaches, anesthesia, physical therapy, ultrasound technicians, and radiologists. The intraoperative use of low molecular weight dextran for volume expansion was not controlled by the protocol.

Poller et al. used 1 mg of warfarin given daily to patients with no past history of DVT undergoing gynecologic surgery and found results similar to ours [5]. Wilson et al. examined the efficacy of 2 mg of warfarin given daily versus adjusted variable-dose warfarin given for 1 month following hip or knee reconstructive surgery and found no difference in the incidence of DVT after one month [6].

Not all published studies have reached our conclusions. Fordyce et al. studied 148 patients having primary hip replacement, receiving 1 mg of warfarin for 1 week preoperatively and then 3 weeks postoperatively versus control of no anticoagulant [7]. Radioactive iodinated fibrinogen scan was the survey technique for DVT, with confirmation by venography for positive scans. In that study, 34% of patients receiving warfarin and 26% patients in control group had DVT. Dale et al., in a study of 35 patients having hip replacements for unreported causes, found a 40% incidence of DVT detected by venograms by the 10th postoperative day [8]. They had received 1 mg of warfarin for 8–28 days preoperatively and then daily for 7–10 days. Also, studies of patients receiving variable-dose warfarin and having prolonged PT's have been reported as having had a given incidence of DVT and/or PT [9–12]. The difference between these and our currently reported study may be explained by the clarity of our study. In other studies there were a number of surgeons involved (many of whom were still in training), exclusions with prior DVT or hip surgery, and differences in detection techniques.

Pneumatic compression stockings were not used in

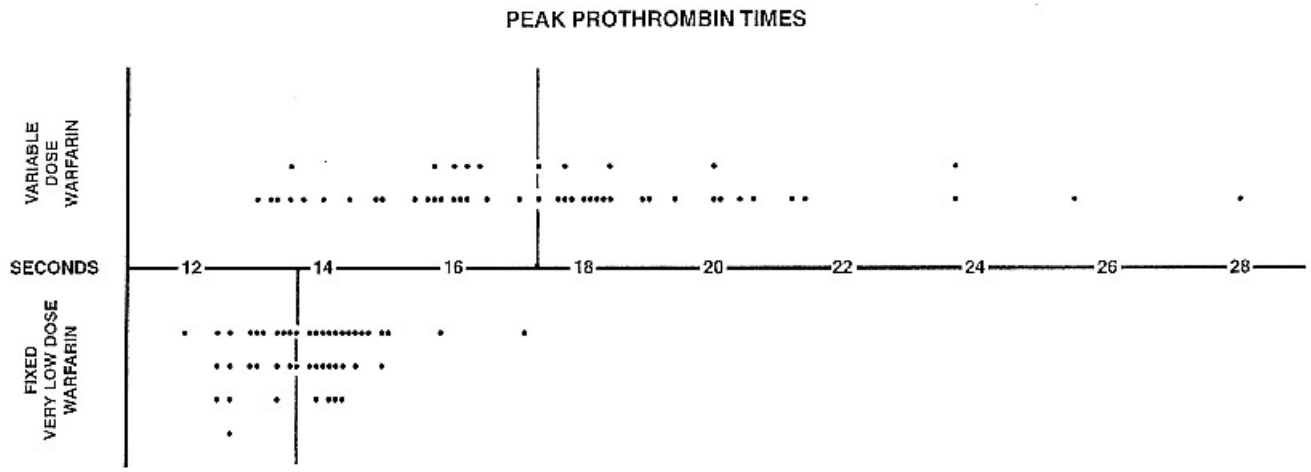

Fig. 1. Peak prothrombin times of patients receiving variable-dose warfarin and those receiving fixed, very low dose (1 mg) warfarin (sec). Median value demonstrated by vertical bar.

either arm of this study. These stockings are known to decrease the venous stasis time in the lower extremities and to activate fibrinolysis [13–15]. This would create another, albeit possibly useful, perturbation of the coagulation system. They are not adequate when used alone for prophylaxis against DVT following hip surgery [14–17]. Compression stockings alone are not as effective as is variable-dose warfarin started preoperatively [18]. It would be reasonable to add compression stockings to our fixed low-dose warfarin regimen in future studies.

The conclusions from this study need to be considered when considering the recommendations of the 1995 ACCP Consensus Conference on Antithrombin Therapy, namely, that patients undergoing elective hip replacement be given unmonitored, twice daily, low molecular weight heparin (LMWH), monitored warfarin (INR 2.0–3.0), or preoperative low-dose unfractionated heparin with postoperative adjustments to maintain the PTT in the upper range of normal [19]. The conference concluded that the final selection depends on efficacy, cost, and convenience. The report also referenced the advantage of spinal or epidural anesthesia or regional block for prevention of DVT [20]. It added that either elastic or pneumatic compression stockings should be added to enhance the efficacy of whichever drug is used.

There was no evidence of increased bleeding at the time of surgery among patients receiving fixed very low dose warfarin. Most patients had no change of PT. There were, nevertheless, exceptions, based upon variables of nutrition, pharmacokinetics of warfarin, and co-administered drugs. Thus, there is a reduced need to monitor the PT, perhaps to every other or every third day.

The mechanism for activity of this low-dose regimen must be studied further. We have previously demonstrated that the regimen causes no change in functional levels of factors II, VII, IX, and X, or protein C [3]. It is possible that low-dose warfarin dampens the propensity for pathologic thrombosis. One mechanism for this would be by reducing the posttranslational number of γ-carboxyglutamic acid residues placed onto the parent molecules of factors II, VII, IX, and X [21–31]. Protein Z has not been measured. Low-intensity warfarin suppresses prothrombin fragment F1+2 and the thrombin-antithrombin (TAT) complex in patients with 2- to 4-sec prolongation of PT undergoing lower extremity orthopedic surgeries [32]. Li et al. reported that most patients with INR values of 1.2–1.7 had a decrease of F1+2 compared to healthy controls [33]. They reported that the reduction of F1+2 was not proportional to the intensity of warfarin therapy as reflected in the PT. Takano et al. found a significant reduction in TAT concentration at low levels of warfarin-induced anticoagulation (INR 1.72 ± 0.07), with no correlation between INR and TAT [34]. There is no clear relationship between intensity of therapy and other markers of activated coagulation β-thromboglobulin and D-D dimer in patients receiving low-intensity warfarin [35].

Venograms have been the traditional technique for detecting proximal and distal DVT. While contrast venography is accurate in skilled hands, it remains an invasive procedure with potential complications of pain, renal dysfunction, anaphylaxis, and procedure-related venous thrombosis [36]. Moreover, accuracy of venograms can be adversely impacted by the adequacy of venous filling by contrast, muscle relaxation of the patient, flow artifacts, and the experience of the radiologist [37]. Even in centers with a great deal of experience, 10–30% of venograms fail to visualize segments of the venous systems. It cannot be performed if patients have dye allergy or poor venous access in the legs, as may occur with edema [38–42]. For these reasons, and because this study would have required 3 venograms, we used compression Doppler ultrasound for detection of DVT. This was with awareness that we may miss asymptomatic lower-leg

DVT below the trifurcation. While venography can detect small-volume thrombi below the popliteal vein, it should be questioned whether their detection is of enough clinical significance to warrant the risk of the venogram, since it is not likely that such small lesions would cause significant PE or post-phlebitic syndrome [43–47].

Reviews critical of ultrasound as not being adequate for detection of asymptomatic DVT of the leg included early studies [42,52,53]. Initially, ultrasound used only a graded compression technique, evaluating whether the vein walls would coapt [56]. More recent studies have shown that the combination of color Doppler, pulsed Doppler, and compression ultrasonography provides an accurate and reproducible technique for the evaluation of venous thrombotic disease [51,55]. Lewis et al. recently described the use of this technique compared to venography with resultant sensitivity of 95%, specificity of 99%, a positive predictive value of 95% and a negative predictive value of 99%, and an overall accuracy of 98% using color Doppler ultrasound analysis [56]. All of these techniques were applied in our current report.

Kearon et al. reported about 20% of patients with isolated distal leg DVT have extension of their lots to the proximal veins [46–48]. This extension usually occurs within a week [49,50]. Thus, the 1-month follow-up study used in this investigation would capture those patients with earlier nondetected thrombosis.

CONCLUSIONS

This report presents further evidence of clinical efficacy for fixed very low dose warfarin in the prophylaxis against deep venous thrombosis in high-risk settings. This regimen has been shown to work in patients requiring indwelling subclavian vein catheters and now in patients receiving hip replacement surgery for degenerative joint disease. This fixed very low dose warfarin therapy, when begun preoperatively, appears to be a useful method for prophylaxis against DVT in these selected patients. This technique appears to be equal to variable-dose warfarin in its efficacy, while being less complicated to administer and less expensive to monitor. The application of this technique must be confined to selected cases with no personal or family history of thrombotic disease and no concomitant predisposing disease such as congestive heart failure or atrial fibrillation.

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