PRACTICES AND PROTOCOLS IN DVT PROPHYLAXIS

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INTRODUCTION

The foot and ankle surgeon's medical management of their patients includes pharmacologic prophylactic measures for thromboembolism of the lower extremity. Surgeons in this field are presented with common risk factors for venous thromboembolism (VTE) and must deal with the consequences of dosing, monitoring, and addressing complications that arise. While studies examining this specialty's role in VTE risk and prevention are few, with those studies reporting a very low incidence of deep vein thrombosis (DVT)[1-3] standard of care often dictates pharmacologic intervention to prophylax in the same manner as major orthopedic surgery. This discussion will focus on the pharmacologic prevention of thrombosis, the laboratory monitoring (specifically warfarin dose adjustment), and associated risks with anticoagulation therapy.

Many patients undergoing elective surgery may be taking anticoagulant therapy because of underlying medical issues such as atrial fibrillation, mechanical heart valves, or previous thromboembolism. Or, those who undergo elective surgery may require long term anticoagulation due to multiple risk factors for venous thrombosis or pulmonary embolus (PE). Often, the primary care physician will assume monitoring responsibility for long term anticoagulation, especially if the patient is already on long term warfarin therapy. However, often the primary care physician will not assume care of anticoagulant monitoring, and the podiatric physician must be medically responsible for such practices. Several options exist for pharmacologic prophylaxis of VTE in any orthopedic surgery. Heparin, low-molecular weight heparin, warfarin, and factor X inhibitors have been proven effective, yet uncertainty still arises as to which therapy to employ, the timing of the therapy, and at what dose.

WARFARIN

Anticoagulation is mediated by inhibition of the vitamin K-dependent coagulation factors II, VII, IX, X, and proteins C and S. The full anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36-72 hours after drug administration.[4,5] Despite a milieu of drug interactions and well documented side-effects, warfarin has been the oral anticoagulant of choice for over 50 years.[5] It is also well known for having a narrow therapeutic range. Excessive or inadequate anticoagulation can lead to severe complications. For most clinical indications, the goal of warfarin therapy is to maintain the International Normalized Ratio (INR) between 2 and 3.[4,5] Two separate studies by the same author found incidence of intracranial hemorrhage increased 5 times in patients with atrial fibrillation as the INR increased above 4.5 and stroke events increased 17 times when the INR fell below 2.[6,7] Other risk factors must also be considered. A study done by van der Meer et al[8] showed a 42% increase in major bleeding (intracranial, GI, and muscle bleeding) episodes for each 1 point increase in the INR. The same study also found bleeding increased significantly with age. A 46% increase for every 10-year increase in age was found as compared with age <40.

For those patients already on warfarin with an INR maintained between 2-3, cessation should take place 3-4 days before the surgery. In a prospective study, White et al[9] found the INR to fall to 1.6 at 2.7 days and 1.2 at 4.7 days. For patients taking warfarin as prophylaxis for a thrombotic event, the INR can be maintained at an average of 1.5, or if they have mechanical heart valves the INR should be maintained at 2.0.[5] If a quicker reversal of warfarin is necessary, as in cases of urgent trauma surgery, the anticoagulant should be withheld and administration of vitamin K should ensue. Dosage of vitamin K varies, but generally should be small, at 0.5 to 1.0 mg intravenously.[5]

Dosing of warfarin after surgery can be started immediately in the postoperative setting. To bridge the gap between surgery and the time to reach therapeutic INR, an anticoagulant with a faster onset should be given.[5-10] A dosage of warfarin 5 mg once daily is most common, but is not the only

option. One study shows that 10 mg on the first day, then resuming 5 mg once daily, reaches therapeutic INR 1.4 days earlier than patients receiving 5 mg for the first dose. There were no significant differences between the 2 groups in recurrent events, major bleeding, survival, or number of INR measurements greater than 5.0.[11]

Lab Monitoring

Laboratory monitoring in warfarin therapy begins with understanding the INR. The INR is independent of differences in sensitivity of various Protime (PT) reagents to the effects of warfarin. The INR is calculated from the following formula:

INR= [Patient PT / Control PT^{ISI}

The International Sensitivity Index (ISI) is determined for each PT reagent and instrument combination. The control PT is the mean normal prothrombin time for the laboratory and is set as such from ≥20 fresh normal plasmas.[5,12]

Lab monitoring is done at 1 week or sooner after initiation of treatment at a lab where blood can be drawn for measurement of the INR. Once the appropriate INR is achieved, the lab value can be checked every 4 weeks unless adverse symptoms arise (Table 1).[5] Other options gaining interest in warfarin monitoring are the point-of-care tests (POCT) that are being used for PT monitoring in oral anticoagulant treatment. Portable monitors are designed to detect clot formation by simply placing a drop of blood on a test strip and inserting the strip into a monitor. In self-testing, a trained patient or relative performs the INR determination using a POCT monitor, then the result is sent to the physician for dose adjustment. In self-management, the patient interprets and adjusts the dosage.[12,13]

Table 1

DOSAGE ADJUSTMENT INDICATIONS

INR above therapeutic range and <5	No significant bleeding	Lower or hold the next dose and monitor frequently; when INR approaches desired range, may resume dosing with a lower dose if INR was significantly above therapeutic range.
INR >5 and <9	No significant bleeding	Omit the next one or two doses, monitor INR and resume with a lower dose when the INR approaches the desired range.
	Other risk factors for bleeding	Omit the next dose and give vitamin K orally ≤5 mg, resume with a lower dose when the INR approaches the desired range. If rapid reversal is needed, then give vitamin K orally 2-4 mg and hold warfarin, expect a response within 24 hours – another 1-2 mg may be given orally if needed.
INR >9	No significant bleeding	Hold warfarin, give vitamin K orally 5-10 mg, expect the INR to be reduced within 24-48 hours. Monitor INR and administer additional vitamin K if necessary. Resume warfarin at a lower dose when INR is in desired range.
Any INR elevation	Serious bleeding	Hold warfarin, give vitamin K 10 mg by slow IV infusion and supplement with fresh plasma transfusion or factor X complex.
Any INR elevation	Life threatening bleeding	Hold warfarin, give prothrombin complex concentrate supplemented with vitamin K 10 mg by slow IV infusion, repeat if necessary. Recombinant factor VIIa is an alternative to prothrombin complex concentrate.

Note: Use of high doses of vitamin K (10-15 mg) may cause resistance to warfarin for up to one week.[5]

FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa, approved for use in thromboprophylaxis after orthopedic surgery. Synthetic pentasaccharides are analogues of the pentasaccharide sequence of heparin, which mediates the binding of heparin to antithrombin, accelerating the rate at which it inactivates coagulation factor Xa. The small size and selective binding determines it will not form complexes with platelet factor 4 and cause heparin-induced thrombocytopenia.[14] Fondaparinux also has a predictable pharmacologic binding profile so it can be dosed without the need of lab monitoring. Fondaparinux does have convenient once-daily dosing of 2.5 mg, but still requires subcutaneous injection. The first dose should be administered at least 6-8 hours postoperatively to avoid increased bleeding risk and dosed a length of 5-9 days for hip or knee replacement, or 4 weeks for hip fracture.[14]

Fondaparinux has not been studied in foot and ankle surgery, but several studies have elucidated the efficacy in knee and hip surgery for VTE prophylaxis.[15-19] A meta-analysis of these studies compared fondaparinux to enoxaparin in 4 multicenter, randomized, double-blind trials of major orthopedic surgery. In this analysis the incidence of VTE was 13.7 % in the enoxaparin group and 6.8% in the fondaparinux group. The better performance of fondaparinux was achieved without increasing the incidence of clinically important bleeding (leading to death, reoperation, or critical organ bleeding).[20]

HEPARIN

Heparin is an effective anticoagulant with a rapid effect in low doses for prophylaxis, usually restricted to the hospital setting. It inactivates a number of coagulation enzymes: thrombin (IIa), Xa, IXa, and XIIa, and requires a plasma cofactor named antithrombin (AT). Only about one-third of an administered dose of heparin binds to AT, and this fraction is responsible for most of its anti-coagulant effect. Its anticoagulant activity varies because of differences in chain length of the molecules, with the higher-molecular weight species cleared from the circulation more rapidly than the lower-molecular-weight species.[21] Limitations of heparin are caused by the binding properties to proteins and surfaces, which results in the variable anticoagulant response and also results in a dose-dependant mechanism of clearance. The anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins.[21,22]

Heparin can be used on an inpatient basis when LMWH is contraindicated, usually because of renal failure. Dosage is started at 5,000 Units subcutaneously 2 hours preoperatively, then 5,000 Units subcutaneously every 8-12 hours post-operatively. This dosage results in 60-70% risk reduction for venous thrombosis and fatal PE.[22] In the same series, the use of low-dose heparin was associated with a small excess of wound hematoma, but there was no statistically significant increase in major bleeding.

LOW MOLECULAR WEIGHT HEPARIN

Low molecular weight heparin, compared with UFH, has less effect on the aPTT while still inhibiting factor Xa and activating AT. The aPTT activity of heparin mainly reflects its antifactor IIa activity. LMWHs are born from heparin by chemical or enzymatic depolymerization producing fragments one-third the size of heparin. So, LMWH has a lower binding capacity to circulating and cellular proteins. LMWH has a longer plasma half-life and better bioavailability at low doses compared with UFH and a more predictable dose response. LMWH is cleared principally by the renal route, and its half-life is prolonged in patients with renal failure, therefore it should be avoided in those patients, or if used, they should be monitored closely. Otherwise, LMWH does not need to be monitored and can be used on an inpatient or outpatient basis. Dosage is given subcutaneously at 30 mg twice daily, or 40 mg once daily when used for prophylaxis. LMWH treatment starts 12-24 hours postoperatively and continues for 7-14 days, or until therapeutic INR is reached when long term oral anticoagulation is planned.[21-23]

Compared with placebo, LMWHs produced a 70-79% risk reduction for venous thrombosis without an increase in major bleeding.[20] Meta-analysis of randomized studies comparing prophylactic LMWH with fixed low-dose or adjusted-dose UFH reported an incidence of venous thrombosis of 15.9% in the LMWH group and 21.7% in the heparin groups, with a lower incidence of proximal

venous thrombosis in the LMWH group. No difference in bleeding between the 2 groups was noted.[21-23]

CONCLUSION

Several different pharmacologic options exist for DVT prophylaxis when operating on the foot and ankle. The monitoring of long-term oral anticoagulation can be managed effectively with a relatively low risk of complication when one is aware of standard procedures and protocols. Other short-term anticoagulation can be used without the need of lab monitoring and has shown to be extremely effective in reducing the rate of thromboembolic events in orthopedic surgery. Further studies are needed to assess the risk and risk reduction with use of pharmacologic prophylaxis in foot and ankle surgery.

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