Current Status of Anticoagulation Therapy After Total Hip and Total Knee Arthroplasty

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Abstract

Postoperative venous thromboembolism in the pelvis and lower extremities is a potentially life-threatening complication in patients undergoing elective total hip and total knee arthroplasty. Numerous pharmacologic methods of prophylaxis have been used in the past with varying degrees of success. Warfarin has been proved effective as a prophylactic agent after total hip arthroplasty but has been less efficacious after total knee arthroplasty. The low-molecular-weight heparins have recently been approved for prophylaxis after total hip and total knee arthroplasty and are an acceptable alternative to warfarin. This new class of drugs appears to have the advantage of predictable subcutaneous bioavailability, which allows less frequent administration and laboratory monitoring and offers a decrease in the occurrence of side effects.

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Postoperative venous thromboembolism in the pelvis and lower extremities is a potentially life-threatening complication in patients who undergo elective total hip and total knee arthroplasty. The incidence of deep vein thrombosis after total hip arthroplasty ranges from 45% to 57%; in 23% to 36% of cases, the condition occurs proximally.[1] Fatal pulmonary embolism occurs in 3% to 6% of patients if prophylaxis is not used after total joint arthroplasty.[1] For total knee arthroplasty, the incidence of deep vein thrombosis ranges from 40% to 84%. In 9% to 20% of cases, the condition occurs proximally.[1]

Pulmonary embolism occurs in 1.8% to 7% of patients and is fatal in 0.7% of cases.[1] The larger thrombi that may form in the iliac, femoral, and popliteal veins after total hip arthroplasty are associated with a higher incidence of embolization and mortality. The recently expounded opinion that pulmonary embolism is not a complication of isolated thrombosis from the calf veins has been challenged, and the need for prolonged anticoagulation of calf thrombi remains an issue of debate.[2] Identification of the safest and most efficacious anticoagulation regimen may make this answer easier. Unfortunately, no one prophylactic regimen has been shown to be effective, safe, inexpensive, and convenient enough that it has gained widespread acceptance.

Both primary and secondary means of prophylaxis against thromboembolic disease are available to the orthopaedic surgeon. Primary prophylaxis refers to the prevention of thromboembolic disease and includes pharmacologic, mechanical, and combination therapies. Secondary prophylaxis refers to the identification and treatment of thromboembolic disease before its progression to a more threatening or serious state. Cuff-impedance plethysmography, ultrasound scanning, fibrinogen-uptake monitoring, and contrast venography are of varying utility in the diagnosis of thromboembolic disease. The sensitivities of cuff-impedance plethysmography and ultrasound scanning are too low for them to be beneficial as widespread screening tools.[3-5] Contrast venography is a sensitive and specific technique for identifying deep vein thrombosis; however, not only is it invasive and expensive, but it can also be associated with potential complications, such as postvenographic phlebitis (which occurs in fewer than 1% of cases).

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The need for effective primary prophylactic measures is emphasized by previous studies documenting that 80% of pulmonary emboli occur without evidence of deep vein thrombosis. Furthermore, two thirds of patients who sustain a fatal pulmonary embolism do so within 30 minutes of becoming symptomatic. Time constraints, cost considerations, and the need for more invasive treatment make secondary forms of prophylaxis much less desirable than primary measures. Easy identification of deep vein thrombosis in asymptomatic patients also remains elusive.

The factors promoting thromboembolic disease have been known for many years. Virchow's triad of stasis, vessel injury, and coagulopathy remains the basis for determining risk of thromboembolic disease. Risk factors in the general population include advanced age, prolonged immobility, and history of thromboembolism, obesity, congestive heart disease, use of oral contraceptives, or malignant disease. Patients who undergo total hip or knee arthroplasty tend to be of advanced age, are subjected to periods of immobilization, and often have concomitant disease processes, especially those affecting the cardiovascular and pulmonary systems. In addition, several factors may be related to the procedure itself. Severe tissue trauma encountered during the operation causes large quantities of prothrombic substances to be released. Manipulation of the limb results in torquing and congestion of the femoral and popliteal vessels, and smaller blood vessels may be damaged by surgical instruments.

The ultimate goal of any prophylactic regimen should be the prevention of death; therefore, assessment of the effectiveness of a prophylactic measure should be based on this criterion.[6] The low incidence of fatal pulmonary embolism makes controlled prospective studies difficult. For this reason, many authors have relied on the incidence of deep venous thrombosis as a measure of the likelihood of fatal pulmonary embolism. Furthermore, it has been shown that thrombi in the proximal veins of the thigh and pelvis have a higher predilection for embolization than more distal thrombi.[1] Ideally, randomized, prospective, blinded trials should be conducted and evaluated with reliable, objective diagnostic means. This article will review the current status of anticoagulation therapy after total joint replacement and will attempt to draw conclusions regarding optimal anticoagulation therapy on the basis of the information currently available.

Warfarin

Warfarin has been in use as an anticoagulant agent in hip surgery for close to 40 years. Although its efficacy has been proved, warfarin is not without risk of bleeding complications. Many physicians abandoned warfarin after initial use because of bleeding complications. Nevertheless, administration of warfarin, alone or in conjunction with other prophylactic means, has long been the standard in total hip arthroplasty and remains one of the more prevalent and effective means of prophylaxis.

Mechanism of Action

Warfarin, a vitamin K antagonist, exerts its anticoagulant effect by inhibiting vitamin K epoxide and possibly vitamin K reductase. This leads to limited carboxylation of vitamin K–dependent proteins (prothrombin, factor VII, factor IX, and factor X). In addition, warfarin limits the carboxylation of proteins C and S by impairing their natural anticoagulant effect.

The observed anticoagulant effect is delayed 24 to 36 hours, representing the time necessary for replacement of the normal clotting factors with the newer decarboxylated factors. Since factor VII has the shortest half-life (6 to 7 hours), the initial anticoagulant effect is caused by the turnover of this factor. The full anticoagulant effect is not realized until 72 to 96 hours, when complete replacement of the other vitamin K–dependent factors occurs. Suppression of the natural anticoagulant protein C takes place early due to its short half-life, which may lead to a prothrombic phase at approximately the time of factor VII inhibition. This may explain both the lack of early anticoagulation induced by factor VII inhibition and the need for heparinization early in warfarin therapy.[7]

Results in Total Hip Arthroplasty

Amstutz et al[6] reviewed the data on 2,838 patients who underwent 3,700 total hip arthroplasty procedures and received warfarin prophylaxis during the period from 1970 to 1990. Patients received a daily dose of 10 mg of warfarin beginning the night of surgery and continuing daily to maintain their prothrombin time in a desired range. The currently recommended target range is 15 to 17 seconds (1.2 to 1.4 times the control value), which is equivalent to an international normalized ratio (INR) of approximately 2.0. (The INR is the ratio between the prothrombin time that would have been obtained if the international thromboplastin reagent had been used and the time obtained with use of the locally available reagent.) Until 1976, when the hospital stay averaged 21 days, prophylaxis was continued until the night before discharge. After 1976, the length of hospitalization dropped, and prophylaxis was continued for a total of 3 weeks postoperatively. Di-

agnostic studies were obtained if clinical suspicion warranted and generally consisted of ventilation-perfusion scanning or venography.

In this study of 3,700 total hip arthroplasties, Amstutz et al found no fatal pulmonary emboli. Nonfatal pulmonary emboli occurred in a total of 21 patients (0.57%). Nine emboli were diagnosed with ventilation-perfusion scans, and five were diagnosed on the basis of clinical findings. The incidence of pulmonary emboli was 2.0% from 1970 to 1973, but dropped to 0.4% in the period from 1973 to 1990. The authors felt that the significant drop in the incidence of pulmonary emboli may have been attributable to earlier ambulation and closer monitoring of prothrombin time. Pulmonary emboli developed 24 to 40 days after discharge in 6 patients who received warfarin for an average of 11.6 days. From 1976 to 1990, no emboli were reported in patients who received a 3-week course of warfarin. In the same period, bleeding complications occurred in only 1.6% of the operations; this represented a reduction from the incidence of 4.7% earlier in the study period, which was attributed to maintenance of a lower prothrombin time.

The effectiveness and safety of low-dose warfarin has led to its use after discharge. Paiement et al[8] concluded that adjusted-low-dose warfarin was efficacious and safe in preventing fatal pulmonary emboli after discharge. Their study included 268 patients who underwent total hip arthroplasty and received maintenance warfarin therapy for 12 weeks after discharge. The treatment protocol included careful monitoring to ensure that the prothrombin time remained between 14 and 16 seconds and the partial thromboplastin time was less than 50 seconds, as well as vigilance for potential drug interactions and a daily review of the patient's response to warfarin. Two nonfatal emboli were identified before discharge. No pulmonary emboli or major bleeding episodes requiring treatment occurred after discharge.

The use of a fixed-low-dose regimen of warfarin after discharge may encourage more widespread post-discharge prophylaxis due to its cost-effectiveness, convenience, and less extensive need for monitoring. Wilson et al[9] conducted a randomized study comparing a fixed dosage (2 mg/d) with an adjusted dosage in two groups of patients and found no differences in the incidence of thrombi. A larger study population is required, however, to obtain conclusive results.

Improved understanding of laboratory monitoring allows improved management of the antithrombotic activity of warfarin. Use of the INR would make possible more standardized reporting of anticoagulant effects from institution to institution.[7] The current goal is an INR value of 1.8 to 2.5. Also relevant is the finding by Paiement et al[4] that a small subset of patients receiving low-dose warfarin had an increased risk for bleeding complications, as indicated by an elevated partial thromboplastin time.[4] The incidence of bleeding complications was 26.4% in patients with a partial thromboplastin time over 50 seconds, compared with only 4.5% in those with a time of less than 50 seconds. The cause of this disparity remains unknown; however, there appears to be justification for monitoring both the prothrombin time and the partial thromboplastin time in the initial 7 to 10 days of warfarin therapy.

Results in Total Knee Arthroplasty

The use of warfarin as a prophylactic agent in patients undergoing total knee arthroplasty has not been extensively evaluated.[10] Most of the information concerning the role of warfarin as a prophylactic agent in total knee arthroplasty has been extrapolated from data obtained in patients undergoing total hip arthroplasty. Stulberg et al[2] reviewed 638 total knee arthroplasties in 517 patients, 17 of whom received warfarin for deep vein thrombosis prophylaxis. The overall incidence of thrombus formation was 53%. Two patients had proximal thrombi. Recently, data have become available from five large multicenter, randomized, controlled studies examining various prophylactic agents, in which warfarin was used as a control.[1] The reported incidence of venographically proved deep vein thrombosis varied between 38% and 55% for warfarin, with proximal thrombi occurring in 7% to 12% of patients.

Aspirin

Pharmacologic agents that alter platelet function are appealing to the clinician because of the simplicity of administration, limited bleeding complications, and cost-effectiveness. In the past, arterial, but not venous, thrombi were thought to be due to platelet aggregation. More recently, investigators have reported aggregates of platelets in venous thrombi, suggesting a basis for aspirin as a prophylactic agent.

Mechanism of Action

Aspirin irreversibly binds and inactivates cyclooxygenase in circulating platelets as well as those forming in megakaryocytes. Through inhibition of cyclooxygenase, aspirin inhibits production of thromboxane, a prostaglandin necessary for platelet aggregation. Cyclooxygenase is also present in endothelial cells, where it is involved in the production of prostacyclin, a platelet-aggregation inhibitor. Available data suggest that platelet cyclooxygenase is very

sensitive to aspirin, whereas vascular cyclooxygenase is less sensitive.

Results in Total Hip Arthroplasty

Several studies have been undertaken to examine the efficacy of aspirin prophylaxis in total hip arthroplasty. Initially, low-dose aspirin (1.2 g/d) was found to be as efficacious as warfarin or dextran in preventing proximal thrombosis and pulmonary embolism, although less effective than either warfarin or dextran in reducing the overall number of thrombi formed. This fact, combined with the lower incidence of bleeding complications, led to the conclusion that aspirin is as effective as warfarin or dextran. However, other studies have concluded that aspirin prophylaxis is ineffective in patients undergoing total hip arthroplasty, citing an incidence of deep vein thrombosis as high as 80% in patients who received aspirin in a dosage of 1.2 g/d. The combined results from a number of studies have indicated that the protective effect of aspirin is greater in men than in women.

The observation that inhibition of prostaglandin synthesis occurs with a lower dose of aspirin than does prostacyclin inhibition led to studies regarding the optimum dosage necessary for effective prophylaxis. No significant difference was found in the protective effects of low-dose aspirin (1.2 g/d) compared with high-dose aspirin (3.6 g/d) in the total patient population or according to sex.

While the incidence of deep vein thrombosis is the yardstick by which most studies determine efficacy, it may be preferable to determine the incidence of pulmonary embolism, alone or in conjunction with thrombosis. McCardel et al[11] conducted a prospective study to determine the latter with aspirin prophylaxis (1.3 g/d) in 159 patients who underwent total hip arthroplasty. No symptomatic deep vein thromboses were observed. Of the nine asymptomatic deep vein thromboses found on ultrasound, five were femoral thrombi, and four were calf thrombi. No fatal pulmonary emboli occurred; however, on the basis of the findings on ventilation-perfusion scanning, 20 patients (12.6%) were considered to have a high probability of embolism. Of all patients, 1.9% had symptomatic pulmonary emboli, which compares favorably with the results with other methods of prophylaxis.

Results in Total Knee Arthroplasty

McKenna et al[12] conducted a prospective study examining the incidence of thromboembolic disease after total knee arthroplasty. Patients with rheumatoid arthritis, who were treated with a relatively large dose of aspirin (3.5 g/d), were found to have a lower incidence of disease than patients with osteoarthritis, who took no aspirin or a lower dose of aspirin. A follow-up study concluded that the high incidence of thromboembolic disease after total knee arthroplasty can be reduced with high-dose aspirin (1.3 g three times a day), but not with a low-dose regimen (325 mg three times a day). Although this was a randomized prospective study, it involved only a small number of patients, most of whom were women. A higher dose of aspirin may be necessary to achieve adequate anticoagulation in female patients. The role sex plays in the relative effectiveness of various doses of aspirin in preventing thromboembolic disease remains to be determined.

Standard Unfractionated Heparin

Standard unfractionated heparin can be administered in a fixed low dose or an adjusted dose. Fixed-low-dose heparin has been shown to be less effective than other pharmacologic agents available in the prevention of thromboembolic disease after total hip arthroplasty. Adjusted-dose heparin has been used with varying degrees of success, but its administration is as labor-intensive as use of warfarin is.

Mechanism of Action

Standard unfractionated heparin is a naturally occurring mucopolysaccharide with a mean molecular weight of 12,000 to 15,000 daltons. It is usually obtained from either bovine or porcine intestinal mucosa. Unfractionated heparin acts by binding to antithrombin III, a natural inhibitor of the coagulation cascade, thereby forming a complex that inhibits a number of clotting factors, particularly factors IIa and Xa. The ratio of anti-Xa activity to anti-IIa activity for unfractionated heparin is 1:1. The increased activity of antithrombin III can be monitored by following the activated partial thromboplastin time, because of the significant effects of unfractionated heparin on antithrombin IIa.

Unfractionated heparin has poor bioavailability (approximately 30%), a short half-life (1 hour), and poor clearance mechanisms, necessitating subcutaneous administration up to three times a day. Frequent monitoring of the activated partial thromboplastin time is therefore required to achieve optimal therapeutic effects while avoiding dangerously elevated concentrations. Because reversible thrombocytopenia occurs in about 10% of patients taking the drug, frequent monitoring of the platelet count is necessary as well.

Results in Total Hip Arthroplasty

The failure of low-dose heparin to provide adequate protection from thromboembolism in total hip arthroplasty led to the investigation

of adjusted-dose heparin. Leyvraz et al[13] determined that larger doses of heparin are necessary to reduce the risk of thromboembolism. The results obtained with fixed-dose heparin (3,500 IU every 8 hours) were inferior to those obtained with a dosage adjusted to maintain the partial thromboplastin time between 31.5 and 36 seconds. Deep vein thrombosis was diagnosed by venography in 39% of the patients in the fixed-dose group, compared with only 13% in the adjusted-dose group. There was no difference between the two groups in blood requirements or the incidence of wound hematomas. Although adjusted-dose heparin has been shown to be effective, its administration and maintenance require a higher degree of vigilance and are more time consuming and labor-intensive. Alternative methods of anticoagulation can provide a lower rate of bleeding complications and greater ease of management.

Low-Molecular-Weight Heparins

A number of fractionated constituents can be derived from heparin. These low-molecular-weight heparins are formed by individual depolymerization procedures. The molecular weights of these compounds are between 3,000 and 10,000 daltons, compared with 12,000 to 15,000 daltons for unfractionated heparin.[14] The most investigated and utilized low-molecular-weight heparins are enoxaparin, ardeparin, logiparin, fragmin, and fraxiparine.

The pharmacologic properties of low-molecular-weight heparins are entirely different from those of unfractionated heparin. The molecular weight of a heparin constituent is inversely proportional to its anti-Xa–anti-thrombin (factor IIa) ratio. The constituent with the lowest molecular weight will have the highest ratio. The anti-Xa–anti-IIa ratio for enoxaparin is 3.6:1; that for unfractionated heparin is 1:1. Other low-molecular-weight heparins have anti-Xa–anti-IIa ratios of 3:1 to 5:1. Their highly predictable pharmacokinetic properties and high bioavailability, as well as the lower associated incidence of thrombocytopenia and their ability to target factor Xa while affecting factor IIa to a lesser extent, make the low-molecular-weight heparins particularly appealing as prophylactic agents.

Mechanism of Action

Circulating thrombin (factor IIa) is needed for local hemostasis at the site of surgery, and inhibition of factor Xa is considered crucial in the prevention of thrombosis. The inhibition of thrombin requires the formation of a bridge between the coagulation enzyme (thrombin) and antithrombin III, which is easily accomplished with the larger molecular size of heparin but not with the low-molecular-weight heparins. This bridge is not necessary for the inactivation of factor Xa. Low-molecular-weight heparins are able to achieve a high anti-Xa activity with a relative lack of anti-IIa effect. Prolongation of the clotting times (prothrombin time and activated partial thromboplastin time) is generally thought to be associated with an increased risk of bleeding. The lack of antithrombin activity with low-molecular-weight heparins produces a minimal effect on the activated partial thromboplastin time as a measure of clotting time compared with unfractionated heparin.

Heparin may also induce its hemorrhagic effect by a mechanism independent of its antithrombin III effect. This anti–platelet aggregation effect has been studied ex vivo and in animal models. The low-molecular-weight heparins exhibit significantly less effect on platelets than does unfractionated heparin. Enoxaparin has been shown to have one tenth the anti–platelet aggregation activity of unfractionated heparin ex vivo.

The pharmacokinetic properties of low-molecular-weight heparins are highly predictable after subcutaneous administration. The bioavailability in terms of anti-Xa activity is over 90%, which is approximately three times that of unfractionated heparin. The half-life of low-molecular-weight heparins can vary between 3 and 18 hours, depending on the specific agent used, compared with 1 hour for unfractionated heparin. The primary route of excretion appears to be renal. While unfractionated heparin has saturable mechanisms in its routes of excretion, low-molecular-weight heparins appear to have an advantage of dose-independent elimination. The favorable pharmacokinetics of low-molecular-weight heparins allow them to be administered subcutaneously twice daily with no requirement to follow drug levels or activity.[14] Levels of low-molecular-weight heparin cannot be measured directly. Anti-Xa activity can be monitored in international units with a clot-based test, but this is used mostly for research purposes and has little clinical application.

Another important concern with the use of heparin is the potential development of idiopathic thrombocytopenia. Clinical studies have shown that the incidence of heparin-induced thrombocytopenia is one third less with low-molecular-weight heparins.[14] It is postulated that the decreased incidence may be secondary to the lower molecular weight of these compounds. It is still recommended that a complete blood cell count (including platelets) and a stool test for occult blood be obtained periodically in patients receiving low-molecular-weight heparin therapy.

Results in Total Hip Arthroplasty

A significant reduction in the overall incidence of thrombus formation has been demonstrated with use of the various low-molecular-weight heparins when compared with placebo. Turpie[15] reported a randomized, double-blind study of 100 patients who underwent elective total hip arthroplasty. Venous thrombosis occurred in 10.8% of patients who received enoxaparin and 53.3% of those who received placebo (P = 0.0002). Proximal vein thrombosis occurred in only 4% of the treated group, compared with 20% of the placebo group (P = 0.014). The incidence of bleeding complications was reported as 4% for both groups.

Similar reductions in the overall incidence of thrombosis have been reported from studies of other low-molecular-weight heparins, such as fragmin (16%) and logiparin (32%).[16,17] These studies found no significant differences in the incidence of perioperative bleeding, postoperative bleeding, or transfusion requirements. The higher incidence of thrombosis in the study by Lassen et al[17] may have been due to the decreased daily dosage of anti-Xa used. There does not appear to be an increase in bleeding complications with the use of higher daily anti-Xa dosages. Anti-Xa monitoring was not performed in these studies, demonstrating that monitoring is not necessary to maintain safe administration.

Additional studies have proved enoxaparin, fragmin, logiparin, and fraxiparine superior to both dextran and unfractionated heparin.[18-20] The incidence of bleeding complications was less than or equal to that in patients treated with dextran or unfractionated heparin. Comparisons between studies are difficult, however, as they used agents with different anti-Xa effects.

The popularity of low-molecular-weight heparin in Europe eventually led to clinical trials in the United States, which established the effectiveness of postoperative administration and the superiority of twice-daily dosing. Subcutaneous administration of 30 mg of enoxaparin twice daily has been shown to be superior to a thrice-daily dosage of unfractionated heparin, as well as to once-daily administration of 40 mg of enoxaparin, in the overall prevention of thrombi.[18-20] The incidence of proximal vein thrombosis was not significantly different between the three treatment groups. Major and minor bleeding episodes and total transfusion requirements were comparable in all three groups. It had been considered earlier that dosages lower than 30 mg twice a day or 40 mg once a day were not efficacious, but twice-daily dosing now appears to be the optimal dosing regimen. Once-daily dosing subjects the patient to higher peak anti-Xa levels, which may be associated with a higher risk of hemorrhagic side effects.

Low-molecular-weight heparin has been shown to be as efficacious as warfarin or more so in preventing thromboembolic disease after total hip arthroplasty. Ardeparin administered in a twice-daily regimen was found to be equally effective and safe compared with warfarin.[21] The transfusion rates and incidence of bleeding episodes were not significantly different between the groups. However, there is a higher incidence of bruising around the subcutaneous injection site with low-molecular-weight heparin. The twice-daily regimen was superior to the once-daily regimen, and safety appeared to be equal for all three regimens. In addition, low-molecular-weight heparin did not require the laboratory monitoring and dose adjustments that warfarin required.

Results in Total Knee Arthroplasty

Although most studies have involved patients undergoing total hip arthroplasty, studies examining the efficacy of low-molecular-weight heparin after total knee arthroplasty are becoming available. Leclerc et al[22] conducted a randomized, double-blind evaluation of administration of 30 mg of enoxaparin every 12 hours or placebo in 131 patients after major knee surgery (total knee arthroplasty and tibial osteotomy). Deep vein thrombosis was detected by venography in 65% of the placebo group and 19% of the enoxaparin group (P<0.0001). Proximal deep vein thrombosis was diagnosed in 17% of the patients who received placebo and in no patients who received enoxaparin (P<0.001). The rates of bleeding complications were not significantly different, occurring in 8% of the placebo group and 6% of the enoxaparin group. The authors concluded that a twice-daily fixed-dose postoperative regimen of enoxaparin is effective and safe for reducing the frequency of deep vein thrombosis after major knee surgery.

Patients who underwent total knee arthroplasty in the study by the RD Heparin Arthroplasty Group[21] were divided into three groups. Group I consisted of 150 patients who received ardeparin in a twice-daily dose of 50 U per kilogram of body weight. Group II comprised 149 patients who received ardeparin in a once-daily dose of 90 U / kg. Group III consisted of 147 patients who received warfarin. The incidence of deep vein thrombosis in group I was 26%, with 6% of cases occurring proximally; in group II, 29% (5% proximal); in group III, 43% (10% proximal). The difference between the twice-daily ardeparin regimen and the warfarin regimen was significant (P = 0.004), as was the difference between the twice-daily and once-daily ardeparin regimens (P = 0.04). The transfusion rates and rates of bleeding complications were not significantly different between groups. The authors concluded that low-molecular-weight heparin is significantly more

efficacious than warfarin in total knee arthroplasty. In addition, the low-molecular-weight heparins do not require the laboratory monitoring and dose adjustments that warfarin requires.

Another recent finding associated with the use of low-molecular-weight heparins is their ability to actually treat established deep vein thrombosis. The venographic scores of patients with recent deep vein thrombosis in the lower extremities showed significant reductions after 10 days of enoxaparin therapy (2 mg/kg per day in two divided doses). The implications of these findings may result in the eventual acceptance of low-molecular-weight heparin as a treatment modality as well. This would enable one to continue administration of low-molecular-weight heparin after surgery as an effective treatment for deep vein thrombosis. Because it is easy for patients to administer and requires no monitoring, a low-molecular-weight heparin would be ideal for use on an outpatient basis.

Length of Prophylaxis

Pulmonary emboli can occur after discharge, despite early ambulation. Amstutz et al[23] reported that there were five such cases before 1976. All emboli occurred between 24 and 40 days postoperatively. The same study demonstrated that the desired level of anticoagulation was reached 5 days after beginning warfarin therapy. Although this length of time may be of some concern, warfarin has proved efficacious in providing protection against thromboembolism before the prothrombin time reaches the so-called therapeutic range. With the decreasing length of hospitalization, an efficacious, simple, and cost-effective strategy for home prophylaxis may be indicated.

As previously mentioned, in the study by Amstutz et al[23] there were no emboli after discharge when warfarin therapy was continued for 3 weeks postoperatively. Wilson et al[9] conducted a randomized prospective study to compare the efficacy and safety of fixed-low-dose warfarin (2 mg/d) and a standard higher adjusted dose of warfarin continued for 1 month postoperatively. They found no therapeutic difference between fixed-low-dose warfarin and the higher adjusted dose.

Low-molecular-weight heparin appears promising for outpatient prophylaxis, but until studies currently under way are completed, its efficacy remains unsubstantiated. A particular advantage is that therapeutic-level monitoring would be unnecessary after discharge, unlike the situation with outpatient administration of warfarin.

As the length of hospital stay is rapidly decreasing and the period for prophylaxis in the hospital setting becomes shorter, concerns regarding thromboembolic disease after discharge increase. At this time, however, there are insufficient data to support the widespread routine use of pharmacologic prophylaxis after discharge. No controlled, randomized studies have been performed to establish whether there are benefits to prolonged outpatient treatment, whether these benefits outweigh the potential risks, and whether such a strategy is cost-effective. One must balance the risks of the disease with the risks of treatment. Clinical trials currently in progress may provide the information physicians need to make rational decisions based on objective scientific evidence.

Current Usage of Pharmacologic Agents

A survey of practicing orthopaedic surgeons conducted by Janku et al[24] in 1992 indicated that most surgeons (92%) currently use a pharmacologic agent as a means of prophylaxis after total hip arthroplasty, compared with only 75% in 1986. Therefore, it appears that this form of prophylaxis is extremely popular. The agents typically employed were warfarin and adjusted-dose and low-dose unfractionated heparin. Aspirin was also used occasionally; low-molecular-weight dextran, rarely. The most widely used pharmacologic agent in total hip arthroplasty was low-dose warfarin (over 50% of respondents).

This trend in pharmacologic prophylaxis has changed since a 1986 survey, in which aspirin was reportedly used as often as warfarin in "high-risk" hip arthroplasty patients and was the most predominant form of prophylaxis in those considered at "low risk" (used in over 60%). Fewer orthopaedic surgeons currently use aspirin as their primary agent for prophylaxis. Of the surgeons surveyed, 18% continued prophylaxis for an average of 4 weeks postoperatively, and 60% continued prophylaxis for high-risk patients for an average of 6 weeks. Long-term prophylaxis was for the most part provided by administration of low-dose warfarin on an outpatient basis.

Warfarin has been proved effective as a prophylactic agent after total hip arthroplasty. The results after total knee arthroplasty have not been as adequately demonstrated, as the rates of deep vein thrombosis have ranged from 38% to 55% in controlled, randomized trials.[1,21] There is less consensus for aspirin. Some protective effect against proximal thrombi may be present in men over 40 years of age without previous thromboembolic disease. The protective effect in women appears less satisfactory. The low incidence of pulmonary embolism in all studies reviewed, however, lends support to the efficacy of aspirin as a prophy-

lactic agent. Adjusted-dose heparin is effective in reducing the incidence of deep vein thrombosis, but it carries a higher incidence of bleeding complications, is more difficult to manage, and can be expensive.

Low-molecular-weight heparin prophylaxis is an acceptable, if not superior, alternative to heparin and warfarin prophylaxis. The agents in this new class of drugs possess superior and predictable subcutaneous bioavailability, which allows a less frequent dosing schedule and decreased laboratory monitoring and is associated with a lower incidence of side effects. Ongoing studies are investigating the use of low-molecular-weight heparins to treat established deep vein thrombosis. Considering the current popularity of pharmacologic prophylaxis after total hip and knee arthroplasty and the advantages of low-molecular-weight heparins over traditional pharmacologic agents, these agents have the potential to become the prophylactic agent of choice against deep vein thrombosis.

The Prevention of Thromboembolism Task Force of the American College of Chest Physicians recently found low-molecular-weight heparin to be the only form of anticoagulation therapy effective for both total hip and total knee arthroplasty.[1] In patients undergoing total hip arthroplasty, twice-daily administration of a low-molecular-weight heparin, low-dose warfarin, or adjusted-dose heparin was superior to other forms of prophylaxis in preventing thromboembolic disease. Aspirin, dextran, and mechanical methods alone were found to be less effective. In patients who underwent total knee arthroplasty, low-molecular-weight heparin was more efficacious than warfarin, aspirin, or heparin.

Summary

Low-molecular-weight heparins appear to have advantages as anticoagulant agents after total hip and total knee arthroplasty in terms of efficacy, safety, cost, and ease of administration and to also have a possible role in outpatient postoperative prophylaxis and treatment of established deep vein thrombosis. Warfarin therapy is less expensive but more difficult to manage. The effectiveness of warfarin as an anticoagulant after total hip arthroplasty cannot be disputed; however, the same cannot be said regarding total knee arthroplasty.[1,21]

Other management strategies are possible and may be required in certain circumstances; however, all variables should be carefully considered. A management strategy should be established for patients undergoing total joint arthroplasty. This should include identification of high-risk patients, cautious transfusion of blood products, pharmacologic prophylaxis with an appropriate agent for total hip or knee arthroplasty, early mobilization, postoperative screening of high-risk patients, and continuing pharmacologic prophylaxis for an appropriate period postoperatively.

References

1. Clagett GP, Anderson FA Jr, Heit J, et al: Prevention of venous thromboembolism. *Chest* 1995;108(suppl):312S-334S.
2. Stulberg BN, Insall JN, Williams GW, et al: Deep-vein thrombosis following total knee replacement: An analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg Am* 1984;66:194-201.
3. Paiement GD, Wessinger SJ, Harris WH: Survey of prophylaxis against venous thromboembolism in adults undergoing hip surgery. *Clin Orthop* 1987;223:188-193.
4. Paiement G, Bell D, Wessinger SJ, et al: New advances in the prevention, diagnosis and cost effectiveness of venous thromboembolic disease in patients with total hip replacement, in Brand RA (ed): *The Hip: Proceedings of the Fourteenth Open Scientific Meeting of the Hip Society, 1986.* St Louis: CV Mosby, 1987.
5. Paiement G, Wessinger SJ, Waltman AC, et al: Surveillance of deep vein thrombosis in asymptomatic total hip replacement patients: Impedance phlebography and fibrinogen scanning versus roentgenographic phlebography. *Am J Surg* 1988;155:400-404.
6. Amstutz HC, Grecula MJ, Dorey F: Prevention of thromboembolic disease with warfarin. *Semin Arthroplasty* 1992;3:99-107.
7. Hirsh J, Dalen JE, Deykin D, et al: Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1992;102(suppl 4):312S-326S.
8. Paiement GD, Wessinger SJ, Hughes R, et al: Routine use of adjusted low-dose warfarin to prevent venous thromboembolism after total hip replacement. *J Bone Joint Surg Am* 1993;75:893-898.
9. Wilson MG, Pei LF, Malone KM, et al: Fixed low-dose versus adjusted higher-dose warfarin following orthopedic surgery: A randomized prospective trial. *J Arthroplasty* 1994;9:127-130.
10. Hodge WA: Prevention of deep vein thrombosis after total knee arthroplasty: Coumadin versus pneumatic calf compression. *Clin Orthop* 1991;271:101-105.
11. McCardel BR, Lachiewicz PF, Jones K: Aspirin prophylaxis and surveillance of pulmonary embolism and deep vein thrombosis in total hip arthroplasty. *J Arthroplasty* 1990;5:181-185.
12. McKenna R, Galante J, Bachmann F, et al: Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *Br Med J* 1980;280:514-517.
13. Leyvraz PF, Richard J, Bachmann F, et al: Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 1983;309:954-958.

14. Leizorovicz A, Haugh MC, Chapuis FR, et al: Low molecular weight heparin in prevention of perioperative thrombosis. *Br Med J* 1992;305:913-920.
15. Turpie AGG: Enoxaparin prophylaxis in elective hip surgery. *Acta Chir Scand Suppl* 1990;556:103-107.
16. Tørholm C, Broeng L, Seest Jørgensen P, et al: Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery: A placebo controlled study. *J Bone Joint Surg Br* 1991;73:434-438.
17. Lassen MR, Borris LC, Christiansen HM, et al: Prevention of thromboembolism in 190 hip arthroplasties: Comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991;62:33-38.
18. Levine MN, Hirsh J, Gent M, et al: Prevention of deep vein thrombosis after elective hip surgery: A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991;114:545-551.
19. Danish Enoxaparin Study Group: Low-molecular-weight heparin (enoxaparin) vs dextran 70: The prevention of postoperative deep vein thrombosis after total hip replacement. *Arch Intern Med* 1991;151:1612-1624.
20. Colwell CW Jr, Spiro TE, Trowbridge AA, et al: Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement: A clinical trial comparing efficacy and safety. *J Bone Joint Surg Am* 1994;76:3-14.
21. RD Heparin Arthroplasty Group: RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. *J Bone Joint Surg Am* 1994;76:1174-1185.
22. Leclerc JR, Geerts WH, Desjardins L, et al: Prevention of deep vein thrombosis after major knee surgery: A randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost* 1992;67:417-423.
23. Amstutz HC, Friscia DA, Dorey F, et al: Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. *J Bone Joint Surg Am* 1989;71:321-326.
24. Janku GV, Paiement GD, Green HD: Prevention of venous thromboembolism in orthopaedics in the United States. *Clin Orthop* (in press).