Prevention of Deep-Vein Thrombosis After Total Knee Arthroplasty in Asian Patients

Comparison of Low-Molecular-Weight Heparin and Indomethacin

By Ching-Jen Wang, MD, Jun-Wen Wang, MD, Lin-Hsiu Weng, MD, Chia-Chen Hsu, MD, Chung-Cheng Huang, MD, and Pao-Chu Yu, MD

Investigation performed at the Departments of Orthopedic Surgery and Diagnostic Radiology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Background: A prospective clinical study was performed to compare the efficacy of low-molecular-weight heparin and indomethacin for the prevention of deep-vein thrombosis after total knee arthroplasty in Asian patients.

Methods: One hundred and fifty patients undergoing total knee arthroplasty were randomly divided into three groups. One group consisted of fifty-one patients who received no prophylaxis with an anticoagulant (the control group), one consisted of fifty patients who received the low-molecular-weight heparin Fraxiparine (the Fraxiparine group), and the third consisted of forty-nine patients who received indomethacin (the indomethacin group). Bilateral ascending venography was performed preoperatively and at five, six, or seven days postoperatively. A third venogram was made at three months for patients who had had a deep-vein thrombosis.

Results: The prevalence of deep-vein thrombosis was 71% in the control group, 50% in the Fraxiparine group (p = 0.042), and 45% in the indomethacin group (p = 0.011). Only 28% of the deep-vein thromboses were symptomatic, and there were no pulmonary emboli.

Conclusions: Compared with no prophylaxis, Fraxiparine and indomethacin significantly lowered the prevalence of deep-vein thrombosis after total knee arthroplasty. Prophylaxis against deep-vein thrombosis in the Asian population appears to be warranted.

Level of Evidence: Therapeutic study, Level I-1a (randomized controlled trial [significant difference]). See Instructions to Authors for a complete description of levels of evidence.

Several recent studies have demonstrated that the prevalence of deep-vein thrombosis after total knee arthroplasty in the Asian population is similar to that in the Western population. However, the locations of the thromboses in Asian patients have differed, with a predominance of distal clots (in the calf) and very few proximal clots (in the thigh or pelvis) or pulmonary emboli. Therefore, the risks of deep-vein thrombosis after total knee arthroplasty have not been fully appreciated and the importance of prophylaxis against this complication has not been emphasized in Asian countries. In contrast to the situation in Western countries, where routine prophylaxis against deep-vein thrombosis is standard practice after total joint replacement, pharmaceutical prophylaxis against deep-vein thrombosis is not routine in most hospitals in the East. Therefore, prophylactic strategies after major orthopaedic procedures remain controversial in the East.

Indomethacin is one of the most commonly prescribed nonsteroidal anti-inflammatory drugs for postoperative analgesia as well as for treatment of arthritic knees in Taiwan. We are not aware of any reports on the efficacy of indomethacin for the prevention of deep-vein thrombosis after total knee arthroplasty. We speculated that, while it is being used as an analgesic, indomethacin might also lower the prevalence of deep-vein thrombosis through its ability to decrease platelet aggregation. Low-molecular-weight heparin is the most commonly used pharmaceutical agent for prophylaxis against deep-vein thrombosis in North America and Europe; however, its efficacy in the Asian population has not been established, to our knowledge. The purpose of this prospective clinical study was to compare the efficacy of a low-molecular-weight heparin (Fraxiparine) and that of indomethacin for the prevention of deep-vein thrombosis after total knee arthroplasty in an Asian population.
Materials and Methods

The institutional review board of our hospital approved the study, and all patients provided informed consent to participate in it. The exclusion criteria included recent thromboembolic disease, a history of a coagulopathy including thrombocytopenia, a history of allergy to iodine, and a technical failure in the performance of venography. From July 2001 to June 2002, 150 patients (118 women and thirty-two men) scheduled to undergo total knee replacement were recruited. The average age (and standard deviation) of the patients was 66 ± 9 years (range, thirty-two to eighty-two years), the average body weight was 67 ± 10 kg (range, 45 to 100 kg), and the average body height was 153.5 ± 7.6 cm (range, 139 to 179 cm).

Seventy-two of the total knee arthroplasties were performed on the right side and seventy-eight, on the left side. Patients were randomly divided into three groups according to the admission schedules. One group consisted of fifty-one patients who received no prophylaxis with an anticoagulant (the control group), one consisted of fifty patients who received Fraxiparine (the Fraxiparine group), and one consisted of forty-nine patients who received indomethacin (the indomethacin group). The dosage of Fraxiparine, which was based on the patient’s body weight, ranged from 1900 IU, or 0.2 mL, to 3800 IU, or 0.4 mL, per day and was given subcutaneously from the day before the surgery to the day of discharge from the hospital. The dosage of indomethacin was 25 mg given orally twice daily starting on the day before the surgery and continuing until the day of discharge from the hospital. The indomethacin was given in suppository form to patients with gastrointestinal intolerance.

The preoperative workup included a complete blood-cell count, coagulation and chemistry profiles, electrocardiography, chest radiographs, and radiographs of the affected knee. Two orthopaedic surgeons (C.-J.W. and J.-W.W.) performed all of the operations with tourniquet control and with the patient under either general or spinal anesthesia. One type of knee prosthesis (Advantim; Wright Medical Technology, Arlington, Tennessee) was used in all patients, and all components were cemented. Intravenous cefamezine was given to all patients for prophylaxis against infection. All patients were managed postoperatively with the same protocol, which included bedside continuous passive motion, physiotherapy with partial weight-bearing on the operatively treated limb, and range-of-motion, quadriceps, and hamstring exercises. In addition, patients were encouraged to perform calf pump exercises bilaterally.

Bilateral ascending venography was performed within one week preoperatively and at five, six, or seven days postoperatively. If the venogram showed positive findings for deep-vein thrombosis, then a repeat venographic study on the affected lower limb was performed at three months. Two radiologists who were blinded to the nature of the study interpreted the results of the venograms. The criteria for the diagnosis of deep-vein thrombosis included an intraluminal filling defect, abrupt termination of the opaque contrast column, and nonfilling of the deep veins proximal to the knee. Any difference in opinion between the radiologists was discussed to reach a consensus before the final report was made. Clinical symptoms suggestive of deep-vein thrombosis, including pain and swelling of the limb, calf tenderness, skin discoloration, venous engorgement, enlargement of the girth of the calf or thigh, the Homans sign, and temperature elevation, were sought daily. A deep-vein thrombosis was defined as symptomatic when symptoms that required treatment developed in a patient with a positive venogram. Each symptomatic
deep-vein thrombosis was graded clinically as mild, moderate, or severe. Patients with severe symptoms were treated initially with intravenous heparin until the symptoms decreased and then with oral warfarin until the symptoms subsided. Patients with mild or moderate symptoms were treated with aspirin. When symptoms suggestive of pulmonary embolism, including chest pain, difficulty breathing, or hemoptysis, developed, additional studies, including arterial blood gas measurement, a chest radiograph, and a perfusion lung scan, were performed.

The data for the Fraxiparine and indomethacin groups were compared statistically with those for the control group and with each other with use of the Mann-Whitney test. Significance was set at p < 0.05.

Results

Venographic studies were performed preoperatively on eighty-three patients (eighty-three operatively treated and eighty-one untreated lower limbs, with two technical failures in the untreated limbs). There were five preoperative deep-vein thromboses in the calf, including four on the operatively treated side and one on the untreated side, but none of the thromboses were symptomatic. The overall prevalence of preoperative deep-vein thrombosis was 3% (five of 164), with 5% (four) in the eighty-three operatively treated limbs and 1% (one) in the eighty-one untreated limbs.

One hundred and fifty patients had venographic studies performed in the first postoperative week. A positive deep-vein thrombosis was noted in eighty-three (55%) of the 150 operatively treated limbs and twenty-one (14%) of the untreated limbs. Ninety-four percent of the eighty-three deep-vein thromboses in the operatively treated limbs were in the calf veins, 6% were in the popliteal vein, and none were in the femoral or iliac vein. Twenty-eight percent (twenty-three) of the eighty-three clots in the operatively treated limbs were symptomatic, and none of the clots in the untreated limbs were symptomatic. The prevalences and locations of the deep-vein thromboses in the operatively treated limbs are summarized in Table I. The prevalence of deep-vein thrombosis was 71% (thirty-six of fifty-one) in the control group, 50% (twenty-five of fifty) in the Fraxiparine group (p = 0.042), and 45% (twenty-two of forty-nine) in the indomethacin group (p = 0.011). There was no significant difference, with the numbers available, between the Fraxiparine and indomethacin groups with regard to the prevalence of deep-vein thrombosis (p = 0.616). Symptoms were associated with 42% (fifteen) of the thirty-six deep-vein thromboses in the control group, 16% (four) in the Fraxiparine group (p = 0.035), and 18% (four) in the indomethacin group (p = 0.067). There was no significant difference, with the numbers available, between the Fraxiparine and indomethacin groups with regard to the prevalence of deep-vein thromboses that were symptomatic. The five patients with silent deep-vein thrombosis preoperatively also had a positive venogram postoperatively. The size of the postoperative deep-vein thrombosis was the same as the preoperative thrombosis in four patients and was slightly larger in one, but none were clinically symptomatic.

Severe symptoms developed in association with the deep-vein thrombosis in fifteen patients, including nine in the control group, two in the Fraxiparine group, and four in the indomethacin group. Of the fifteen patients, twelve (seven in the control group, two in the Fraxiparine group, and three in the indomethacin group) were initially treated with intravenous heparin for three to five days until the symptoms decreased and then with oral warfarin for four to ten weeks until the symptoms subsided. The dosage of warfarin was monitored by measuring the prothrombin time and international normalization ratio. A prolonged international normalization ratio was found in four patients, but none had a bleeding complication. The remaining three patients, including two in the control group and one in the indomethacin group, were treated with a therapeutic dose of Fraxiparine for seven to ten days. No bleeding complications were noted. Eight patients,

| TABLE II | Prevalence and Location of Deep-Vein Thrombosis Seen on Venograms at Three Months |
|----------|---------------------------------|-------------------------------|-----------------|-----------------|
|          | **Control** | **Fraxiparine** | **Indomethacin** | **Total** |
| No. of patients | 36 | 25 | 20 | 81 |
| Deep-vein thrombosis | | | | |
| No. (%) of patients | 9 (25%) | 7 (28%) | 3 (15%) | 19 (23%) |
| P value | | | | |
| Compared with control group | 0.879 | 0.610 | 0.690 | |
| Location of deep-vein thrombosis | | | | |
| Calf veins | 9 | 7 | 3 | 19 |
| Popliteal vein | 0 | 0 | 0 | 0 |
| Femoral vein | 0 | 0 | 0 | 0 |
| Iliac vein | 0 | 0 | 0 | 0 |
| Pulmonary embolism | 0 | 0 | 0 | 0 |
| Symptomatic deep-vein thrombosis (no. [%] of all thromboses) | 1 (11%) | 1 (14%) | 1 (33%) | 3 (16%) |
including five in the control group, two in the Fraxiparine group, and one in the indomethacin group, underwent a third venographic study at three months. The remaining two patients refused repeat venography. Nineteen of those repeat studies, including nine in the control group, two in the Fraxiparine group, and three in the indomethacin group, revealed a deep-vein thrombosis. All of the thromboses were distal (in the calf veins). At three months, the prevalence of deep-vein thrombosis in patients who had had a deep-vein thrombosis postoperatively, eighty-one (thirty-six in the control group, twenty-five in the Fraxiparine group, and twenty in the indomethacin group) underwent a third venographic study at three months. The remaining two patients refused repeat venography. Nineteen of those repeat studies, including nine in the control group, seven in the Fraxiparine group, and three in the indomethacin group, revealed a deep-vein thrombosis. All of the thromboses were distal (in the calf veins). At three months, the prevalence of deep-vein thrombosis in patients who had had a deep-vein thrombosis postoperatively was 23% (nineteen of eighty-one) overall, with a prevalence of 25% (nine of thirty-six) in the control group, 28% (seven of twenty-five) in the Fraxiparine group (p = 0.879), and 15% (three of twenty) in the indomethacin group (p = 0.610). There was no significant difference, with the numbers available, between the Fraxiparine and indomethacin groups (p = 0.690). The prevalences and locations of the deep-vein thromboses at three months are summarized in Table II. Of the nineteen deep-vein thromboses, three (one in each group) were asymptomatic. These three cases were treated with acetaminophen until the symptoms subsided, with the duration of treatment ranging from two to eight weeks.

There were no systemic complications related to the venography; however, one patient had transient chills. Local complications included pain and numbness of the foot in one patient and leakage of contrast material in another.

Discussion

The effect of low-molecular-weight heparin with regard to the prevention of deep-vein thrombosis in an Asian population has not been established, to our knowledge. The results of this study showed that Taiwanese patients who received prophylaxis with Fraxiparine had significantly fewer deep-vein thromboses and symptomatic deep-vein thromboses after total knee arthroplasty than did the control group. Therefore, low-molecular-weight heparin (Fraxiparine) appears to be effective for prophylaxis against deep-vein thrombosis after total knee arthroplasty in an Asian population.

Conventional nonsteroidal anti-inflammatory drugs, including indomethacin, inhibit platelet aggregation, prolong bleeding time, and decrease the level of serum thromboxane B2. Indomethacin is a commonly prescribed drug primarily used for analgesia postoperatively and as an anti-inflammatory drug for degenerative arthritis. Indomethacin also has the potential for preventing deep-vein thrombosis by decreasing platelet aggregation. The results of this study showed that indomethacin significantly lowered the prevalence of deep-vein thrombosis (p = 0.011) and lowered the prevalence of symptomatic deep-vein thrombosis (p = 0.067) after total knee arthroplasty. The efficacy of indomethacin for the prevention of deep-vein thrombosis after total knee arthroplasty was comparable with that of Fraxiparine in our study group. Therefore, indomethacin appears to have the additional benefit of preventing deep-vein thrombosis while providing postoperative analgesia. The administration of indomethacin is convenient and relatively inexpensive.

In Western countries, the reported prevalence of deep-vein thrombosis after total knee arthroplasty has been consistently high, especially in patients without anticoagulation prophylaxis. Similar findings were reported in Asian populations when venography was performed, however, the rate of proximal clots in the thigh and pelvis has been very low in the Asian population. This study showed that the prevalences of deep-vein thrombosis and symptomatic deep-vein thromboses were higher in the control group than in the patients receiving prophylaxis with either Fraxiparine or indomethacin. However, neither Fraxiparine nor indomethacin totally prevented deep-vein thrombosis.

In conclusion, low-molecular-weight heparin (Fraxiparine) and indomethacin significantly lower the prevalence of deep-vein thrombosis after total knee arthroplasty in an Asian population. There were no pulmonary emboli or deaths in our study, but the series was small. There was a higher prevalence of deep-vein thrombosis, and patients were frequently symptomatic, without pharmaceutical prophylaxis.

References
