A short course of low-molecular-weight heparin to prevent deep venous thrombosis after elective total hip replacement

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Objective: To determine the efficacy of a short course of low-molecular-weight heparin (enoxaparin) in the prevention of deep venous thrombosis and pulmonary embolism after elective total hip replacement.

Design: A prospective cohort study. Follow-up was a minimum of 3 months.

Setting: An acute-care hospital with a large-volume practice of elective total joint replacement.

Patients: A prospective group of 150 patients who required primary total hip arthroplasty and a historic control group of 150 patients. All patients were treated with compression stockings, indomethacin and early mobilization. The treatment group received low-molecular-weight heparin, 30 mg every 12 hours for 5 days postoperatively; the control group received no specific anticoagulant therapy.

Interventions: Total hip replacement. Doppler venography on postoperative day 5 and 2 to 5 days later if required.

Main outcome measures: Presence or absence of deep venous thrombosis. Wound hemorrhage, transfusion rate, number of units of blood transfused and changes in the hemoglobin level.

Results: The incidence of proximal deep venous thrombosis (popliteal vein to common iliac vein) was 0% in the treatment group versus 4% in the control group. There was no difference in bleeding or number of transfusions required. There was, however, a significant ($p = 0.005$) drop in hemoglobin level in the treatment group.

Conclusions: A short course of low-molecular-weight heparin provides effective protection against proximal deep venous thrombosis without significantly increasing the risk to the patient. The treatment is compatible with early patient discharge and the pharmacologic prevention of heterotopic ossification after total joint replacement.

Objectif : Déterminer l'efficacité d'un bref traitement à l'héparine de faible poids moléculaire (énoxaparine) dans la prévention des thromboses veineuses profondes et des embolies pulmonaires après une arthroplastie élective totale de la hanche.

Conception : Étude prospective de cohortes. Le suivi était d'au moins trois mois.

Contexte : Hôpital de soins actifs qui a une importante pratique d'arthroplasties électives totales d'articulations.

Patients : Groupe prospectif de 150 patients qui avaient besoin d'une arthroplastie primitive totale de la hanche et un groupe témoin historique de 150 patients. On a traité tous les patients en leur faisant porter des bas pression, en leur administrant de l'indométhacine et en les faisant marcher rapidement. Les sujets traités ont reçu de l'héparine de faible poids moléculaire, à raison de 30 mg aux 12 heures pendant cinq jours après l'intervention. Ceux du groupe témoin n'ont pas reçu de thérapie particulière aux anticoagulants.

Interventions : Arthroplastie totale de la hanche. Veinographie Doppler cinq jours après l'intervention et de deux à cinq jours plus tard au besoin.

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PRINCIPALES MESURES DES RÉSULTATS : Présence ou absence de thrombose veineuse profonde proximale. Hémorragie à la plaie, taux de transfusion, nombre d'unités de sang transfusées et changements du taux d'hémoglobine.

RÉSULTATS : L'incidence de thrombose veineuse profonde proximale (de la veine poplitée vers la veine iliaque commune) s'est établie à 0 % chez les sujets traités et à 4 % chez ceux du groupe témoin. On n'a constaté aucune différence quant au saignement ou au nombre de transfusions requises. Le taux d'hémoglobine chez les sujets traités a toutefois diminué de façon significative (p = 0,005).

CONCLUSIONS : Un bref traitement à l'héparine de faible poids moléculaire assure une protection efficace contre les thromboses veineuses profondes proximales sans accroître considérablement le risque pour le patient. Le traitement est compatible avec une libération rapide du patient et la prévention pharmacologique de l'ossification hétérotopique après une arthroplastie totale d'une articulation.

Deep venous thrombosis and pulmonary embolism are among the most common and severe complications of total hip arthroplasty. Without prophylaxis, 40% to 60% of patients will have deep venous thrombosis, 15% to 20% a proximal deep venous thrombosis (popliteal vein to common iliac vein) and 0.5% to 2.0% a fatal pulmonary embolism.[1–4] Most would agree that patients with proximal deep venous thrombosis are at significantly greater risk (50%) for symptomatic pulmonary embolism than those with deep venous thrombosis in the calf (1% to 2%) (distal to the popliteal vein).[3,5] However, although deep venous thrombosis of the calf is associated with a low rate of pulmonary embolism, evidence in the literature suggests that in up to 15% of cases the deep venous thrombosis of the calf may propagate, and there is an increased risk of asymptomatic pulmonary embolism with increasing size of the thrombus.[4–7]

Adjusted-dose heparin, low-dose warfarin, and low-molecular-weight heparin are all effective in reducing venous thromboembolic events.[1,4,8,9] Enoxaparin, a low-molecular-weight heparin, has been shown in several randomized clinical trials to be effective and safe in preventing deep venous thrombosis.[10–13] It decreases the rate of deep venous thrombosis to levels of 6% to 20% and proximal deep venous thrombosis as low as 3%.[10,12,13] A combination of the most effective dosing schedule and shortest treatment period of enoxaparin was found to be 30 mg every 12 hours, starting within 24 hours of operation and continuing for 7 days.[10,12] Daily laboratory monitoring of enoxaparin levels is not required. In addition, there is mounting evidence to suggest that enoxaparin may be more cost-effective than the other forms of prophylaxis for deep venous thrombosis.[14,15]

In orthopedic surgery, cost-containment and shorter hospital stay are constantly emphasized. In many institutions the average length of hospitalization for primary total hip arthroplasty is less than 7 days. The objective of this study, therefore, was to determine whether a short course (5 days) of enoxaparin is effective and safe in preventing deep venous thrombosis after elective primary total hip replacement.

PATIENTS AND METHODS

Study design

This study was conducted on a prospective cohort of 150 patients who underwent elective primary total hip arthroplasty between October 1993 and July 1995 and were treated with enoxaparin. A control group comprised 150 patients who underwent total hip arthroplasty between December 1992 and October 1993 but did not receive enoxaparin. All patients were followed up for a minimum of 3 months postoperatively.

Patient profile, surgical and postoperative management

All patients underwent elective primary total hip arthroplasty. Patients 18 years of age or older were eligible. The criteria for exclusion from the study were the following: revision total hip arthroplasty; primary total hip arthroplasty for acute fracture of the proximal femur or acetabulum; previously documented deep venous thrombosis or pulmonary embolism, or both; bleeding disorders; a history of active ulcerative diseases of the gastrointestinal tract; and a history of heparin-induced thombocytopenia.

All patients were operated on by the senior author (J.P.W.). All procedures were done through a posterior approach, with the patient in the lateral position. Patients under the age of 70 years received an uncemented hip (St. Michael's hip), whereas patients aged 70 years or older received a cemented hip (contemporary hip). No surgical drains were used.

Postoperatively, all patients were managed on the same surgical ward, under the supervision of the same head nurse (P.C.). All patients received indomethacin, 25 mg orally 3 times daily for 3 weeks. Postoperative mobilization was standard for all patients as follows: 0 to 24 hours (bed rest), 24 to 48 hours (up to chair), more than 48 hours (ambulate with assistance). In addition, patients wore thromboembolic stockings on both legs until discharged from hospital.

Dosing schedule

Patients were given enoxaparin subcutaneously, 30 mg every 12 hours, starting 12 hours after surgery and continuing for a total of 10 doses or approximately 5 days.

Efficacy and safety outcomes

The presence of deep venous thrombosis, the primary efficacy outcome, was assessed on postoperative day 5 by duplex scanning (B-mode Doppler ultrasonography), a noninvasive vascular examination. All scanning was done by one ultrasonographer, who had 13 years experience in the same laboratory using the same equipment. The ultrasonographer reported the presence or absence of deep venous thrombosis from the calf to the common iliac vein, of both the operated and nonoperated legs.

All cases of proximal deep venous thrombosis were treated with full anticoagulation with intravenous heparin, followed by therapeutic-dose warfarin for 3 months.

All patients with deep venous thrombosis of the calf had repeat duplex scanning on postoperative day 9 to assess the progression of the venous thrombosis. If no progression was noted, the venous thrombosis was not treated and no further scanning was done.

Primary safety outcomes (modified from Colwell and associates[10]) were defined as major bleeding episodes, a perioperative drop in hemoglobin level, the need for a transfusion and serious adverse events, including death, life-threatening episodes and events that resulted in prolonged hospitalization or re-hospitalization. A major bleeding episode was defined as overt hemorrhage associated with at least 1 of the following: death; acute myocardial infarction; a life-threatening event; bleeding from the wound; cerebrovascular accident; retroperitoneal hemorrhage; upper gastrointestinal hemorrhage; or a postoperative transfusion of more than 2 units of packed red blood cells (excluding autologous blood).[10]

Statistical analysis

χ^2 analysis with Yates' correction for continuity was applied to all comparisons of categorical data (rates of deep venous thrombosis). Fisher's exact test was also used for categorical data when cell sizes were too small for χ^2 analysis. A paired *t*-test was used to compare continuous data (operative time in minutes and a drop in hemoglobin level in g/L).

Results

The demographic and operative characteristics of both groups are summarized in Table I. There was no significant difference between the control and enoxaparin groups with respect to age, sex, surgical side (left or right), surgical technique (cemented or uncemented). In the treatment group, 14% (21/150) of the patients missed, on average, 1 dose of enoxaparin. The most frequent reason given by the nursing staff was that "the medication was not available." The mean (and 1 standard deviation) operating time for the control group was 75 (18) minutes (range from 40 to 160 minutes) and for the treatment group 76 (25) minutes (range from 50 to 220 minutes) ($p = 0.75$). There was no significant difference in the proportion of patients in each group who went home or to a rehabilitation hospital ($\chi^2 = 0.93$, $p = 0.34$).

Efficacy

The rate of distal (calf) deep venous thrombosis for the treatment group (15% [22/150]) was not significantly different from that of the control group (12% [18/150]) ($\chi^2 = 0.46$, $p > 0.1$). However, there was a significant difference between the treatment and control groups for the rate of deep venous thrombosis, where 0% (0/150) of the treatment and 4% (6/150) of the control patients had a proximal deep venous thrombosis ($p = 0.03$, Fisher's exact test). These cases of proximal deep venous thrombosis were all treated with intravenously administered heparin, followed by orally administered coumarin for 3 months. Age, sex, surgical side and surgical technique were not confounding. None of the distal thromboses was found to have progressed when scanning was repeated on postoperative day 9.

There were 2 cases of non-fatal symptomatic pulmonary embolism in the treatment group (1.3%) and 1 case in the control group (0.67%) ($p = 1.0$, Fisher's exact test). The case in the control group occurred on postoperative day 3, and the patient was found to have bilateral deep venous throm-

Table I

Demographic Characteristics of Patients in the Control and Treatment (Enoxaparin) Groups

Characteristic	Control ($n = 150$)	Enoxaparin ($n = 150$)
Mean age, yr	60	60
Male/female	68/82	79/71
Left/right hip arthroplasty	78/72	70/80
Cemented/noncemented prosthesis	53/97	59/91

bosis of the calf. The 2 cases of pulmonary embolism in the treatment group occurred 2 and 3 weeks after surgery; both of these patients had negative duplex scans on postoperative day 5.

Safety

There were no major bleeding episodes in the control group and only 1 (0.7%) in the treatment group. There were no deaths or serious adverse events in either group during the postoperative period. The major bleeding episode in the treatment group was a case of upper gastrointestinal bleeding, found on oral gastroduodenoscopy to be caused by gastric erosions. The mean (and 1 standard deviation) perioperative drop in hemoglobin level (measured on postoperative day 3) for the treatment group was 40 (15) g/L (range from 0 to 80 g/L), versus 35 (18) g/L (range from 0 to 90 g/L) for the control group ($p = 0.005$). The homologous transfusion requirement of each group was as follows: 13% (19/150) of the treatment group required more than 2 units of packed red blood cells compared with 7% (11/l50) of the control group ($\chi^2 = 3.32$, $p > 0.05$).

Discussion

The results of this study indicate that a 5-day course of enoxaparin is effective in preventing venous thrombosis after elective primary total hip replacement. Using deep venous thrombosis as at the primary indication for efficacy, we found that enoxaparin significantly reduced the incidence of deep venous thrombosis from 4% in control patients to 0% in the treatment group ($p = 0.03$). These rates of proximal deep venous thrombosis are similar to the lowest reported rates among other studies in the literature.[10,11,16,17] This represents a reduction in the relative risk of symptomatic pulmonary embolism since proximal deep venous thrombosis is associated with the highest risk of pulmonary embolism.[3,5,7] This outcome was achieved with a 5-day course of prophylaxis compared with the 7-day course described in the literature.[10,12] It is significant that the control group also had a rate of proximal deep venous thrombosis similar to that of most treatment groups in the literature. The rate of distal deep venous thrombosis with enoxaparin was 15%, comparable to those found in other studies using the same drug.[10,16,17] The rate of calf deep venous thrombosis for the control group (16%) was similar to that of many reported treatment groups.

On repeat duplex scanning, none of the distal deep venous thromboses in either group progressed. This is in contrast to the findings of Maynard, Sculco and Ghelman[7] who reported a 28% rate of distal thrombus progression after total knee arthroplasty.

There were no cases of fatal pulmonary embolism in either group. There were 2 cases (1.3%) of non-fatal symptomatic pulmonary embolism in the enoxaparin group and 1 case (0.67%) in the control group. These data are consistent with those found in other studies, remembering that there are no studies linking the use of enoxaparin to the prevention of fatal pulmonary embolism in total hip replacement.[13,14]

This study also showed that a 5-day course of enoxaparin is safe when used in the prevention of deep venous thrombosis. There were no major bleeding episodes in the control group and only 1 in the enoxaparin group, a case of upper gastrointestinal bleeding caused by gastric erosions.

There was a significantly larger perioperative drop in hemoglobin level in the enoxaparin group than in the control group ($p = 0.005$), and 13% of enoxaparin and 7% of control patients required more than 2 units of homologous packed red blood cells during their hospitalization.

This is not a randomized controlled study, but rather a prospective cohort using a historic control. The study used duplex scanning (B-mode Doppler ultrasonography) as the primary outcome evaluation. The sensitivity of duplex scanning ranges from 60% to 100%, whereas the specificity is 97%.[10,18–21] However, this test has been shown to be highly technique- and operator-dependent.[22] Depending on the technician, the sensitivity may be increased to 100%, thus bringing the accuracy up to 98%.[22] In the present study, all scans were read by the same technician with 13 years experience using the same equipment. We believe this optimized the sensitivity of the study.

Indomethacin was used in this study as prophylaxis against heterotopic bone formation. Although not studied formally in a human trial in combination with prophylaxis for deep venous thrombosis, indomethacin has been studied in an animal model. This model suggests that low-dose indomethacin may potentiate the antithrombotic effect of low-molecular-weight heparin.[23] Therefore, the presence of indomethacin may have had a confounding effect on the incidence of deep venous thrombosis in both the treatment and control groups.

Conclusions

A 5-day course of enoxaparin is effective and safe in preventing proximal deep venous thrombosis. This dosage schedule might therefore be considered for patients who are to be discharged early from hospital. The control group in this study demonstrates

the potential combined efficacies of early ambulation, antithromboembolic stockings, decreased operative time and nonsteroidal anti-inflammatory agents in reducing the incidence of venous thromboembolism to an acceptable level.

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