Intraoperative heparin in addition to postoperative low-molecular-weight heparin for thromboprophylaxis in total knee replacement

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The administration of heparin during operation has been reported to enhance the efficacy of thromboprophylaxis in patients undergoing total hip replacement. We have performed a small pilot study in which intraoperative doses of heparin were given in addition to the usual postoperative thromboprophylaxis with enoxaparin in 32 patients undergoing total knee replacement. The primary endpoint was deep-vein thrombosis (DVT) as demonstrated by bilateral venography on 6 ± 2 days after operation.

Sixteen patients developed DVT; in two the thrombosis was proximal as well as distal and in one the occurrence was bilateral. There was one major haemorrhage. These results are similar to those obtained with the use of postoperative thromboprophylaxis with enoxaparin alone. They do not provide support for the initiation of a larger randomised trial of this approach to management.

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Deep-vein thrombosis (DVT) occurs in approximately 60% of patients undergoing total knee replacement (TKR) who do not receive thromboprophylaxis.¹ Low-molecular-weight heparin (LMWH), warfarin, or intermittent pneumatic compression reduces this incidence to 10% to 50%, with proximal DVT occurring in 5% to 13% of patients.¹⁻⁶ In a recent trial,⁵ the incidence of DVT was 52% with warfarin and 37% with LMWH (enoxaparin).

In North America, the current preferred method of thromboprophylaxis is the administration of LMWH¹ after surgery. The development of DVT may, however, begin during the operation⁷ and the initiation of thromboprophylaxis before the procedure, as is practised in Europe, or the addition of intraoperative heparin, may reduce the incidence of the formation of thrombus. In 1992, Huo et al⁸ reported a significant reduction in DVT after total hip replacement when intraoperative heparin was added to their standard regime of postoperative prophylaxis with aspirin. We have therefore carried out a small pilot study in patients undergoing TKR to determine whether the use of intraoperative heparin along with postoperative LMWH may have sufficient potential benefit to justify a larger trial.

Patients and Methods

There were 32 patients in the study who were undergoing TKR. Patients were excluded if they had renal insufficiency, significant hepatic dysfunction, a bleeding tendency, defective haemostasis, recent surgery on the eyes, ears or central nervous system, hypersensitivity to heparin, severe hypertension, or weighed less than 40 kg. They were also excluded if they were pregnant, had participated in another drug study in the previous 30 days, or had had a traumatic spinal or epidural tap for anaesthesia. The study was approved by the Research Ethics Board of the Faculty of Medicine of the University of Alberta, and all patients gave informed consent.

Each received an intravenous bolus of 1000 u of unfractionated heparin immediately before operation and after the initiation of epidural or spinal anaesthesia, if used. A second intravenous bolus of 500 u was given at the end of the operation immediately before removal of the tourniquet. They also had routine thromboprophylaxis with postoperative enoxaparin, 30 mg subcutaneously every 12 hours, with the first dose given on the morning after surgery. This was continued for 6 ± 2 days, at which time bilateral venography⁹ was performed. The incidence of DVT as demonstrated by venography constituted the primary outcome measure. Safety was assessed by the incidence of major bleeding, defined as overt bleeding with a decrease in haemoglobin of >20 g/l, intraocular, retroperitoneal, intraspinal or intracranial bleeding, bleeding requiring discontinuation of thrombo-

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Table I. Details of the results in 32 patients who had intraoperative heparin along with postoperative LMWH thromboprophylaxis

	Events	Incidence (%; 95% CI)
Total DVT	16	50 (32 to 68)
Proximal DVT	2	6 (1 to 20)
Major bleeding	1	3 (1 to 16)

prophylaxis, or bleeding complications resulting in reoperation or death. The haemoglobin and platelet counts were measured before entry to the study, on the day of venography, and more often if indicated clinically.

Results

Fifteen patients developed DVT in the operated leg and one bilaterally, an incidence of 50% (95% confidence interval 32 to 68). Two patients had a proximal DVT; in the remainder it was distal only. In one patient, symptoms of DVT occurred on the second day, but in the remainder there were no symptoms. There were no symptomatic pulmonary emboli. There was one major haemorrhage. Ten additional patients had a decrease in haemoglobin of >40 g/l associated with surgery, but without overt postoperative bleeding. These results and their analyses are shown in Table I.

Discussion

The incidence of postoperative DVT in patients undergoing TKR remains very high. We therefore initiated this uncontrolled pilot study to determine if the incidence could be reduced by the addition of intraoperative heparin to the standard regime of postoperative thromboprophylaxis with LMWH, as has been reported for total hip replacement.⁸ The overall incidences of DVT and of proximal DVT were comparable to those in patients having postoperative LMWH thromboprophylaxis alone.²⁻⁶ Although too small to be definite, this pilot study provides little support for the hypothesis that the addition of intraoperative heparin during TKR will give benefits which are clinically significant compared with postoperative thromboprophylaxis with enoxaparin alone. The lower 95% confidence level for total DVT of 32% is well within the range reported for enoxaparin alone. The incidence of bleeding with this approach

may be higher, as evidenced by the considerable decreases in haemoglobin seen in one-third of the patients. Our findings suggest that a significant reduction in the incidence of DVT cannot be obtained by this intervention, and do not support the initiation of a large randomised trial comparing this approach with the use of enoxaparin or other LMWHs alone. Possible explanations for these results, as compared with those reported by Huo et al⁸ for total hip replacement, are the greater potential for thrombosis in patients undergoing TKR and the more effective thromboprophylaxis provided by enoxaparin than by aspirin.¹ To establish a reduction of 50% in the incidence of DVT from the 37% recently reported,⁵ with an α of 0.05 and a power of 80%, would require 100 patients in each arm of a randomised controlled trial. Since our study shows DVT in 16 of 32 patients it is extremely unlikely that one arm of a study including 100 patients could demonstrate an appropriate reduction in event rate of this size.

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