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A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement

M. C. Yoo[1], **C. S. Kang**[2], **Y. H. Kim**[3], **S. K. Kim**[4]

[1] Department of Orthopaedic Surgery, Kyung Hee University Hospital, Hoeki-Dong Dongdaemun-ku, Seoul 130-702, Korea
[2] Keimyung University Dongsang Medical Center 194, Dongsan-Dong, Teague, Korea
[3] Department of Orthopaedic Surgery, Hanyang University Guri Hospital, 249-1, Kyomoon-Dong, Guri, Kyunggi-Do, 471-020, Korea
[4] Department of Orthopaedic Surgery, Korea University Guro Hospital 80, Guro-Dong, Guro-Gu, Seoul, 152-020, Korea

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Summary. *Because of the belief that post-operative deep vein thrombosis (DVT) is rare in Asian patients, thromboprophylaxis is not usually prescribed for surgical patients. This study reports an open multi-centre controlled study of the use of a low molecular weight heparin, nadroparin calcium (Fraxoparine Sanofi France), as opposed to no prophylaxis in 100 patients undergoing uncemented total hip replacement. The patients had bilateral venography performed preoperatively and 10 days after operation. Eight patients (16%) developed DVT in the control group of 50 patients and 1 (2%) in the treatment group, also of 50 patients. Pulmonary embolus occurred in 1 patient in the treatment group and in 3 in the control group. Intraoperative and postoperative blood loss did not differ significantly between the two groups. Our study suggests that the incidence of DVT in Asian patients, though somewhat less than in their Western counterparts, is still considerable. It confirms the safety and efficacy of nadroparin calcium in preventing post-operative DVT in patients undergoing elective total hip replacement.*

Résumé. *A cause de l'idée selon laquelle la thrombose veineuse profonde post-opéraloire est rare parmi les patients asiatiques, la thromboprophylaxie pour les patients opérés est inhabituelle. Nous avons accompli une étude, comparant la prophylaxie au moyen d'héparine de bas poids moléculaire en utilisant du calcium nadroparine (Fraxiparine Sanofi France) et la non-prophylaxie sur 100 patients subissant un remplacement total de la hanche. Les patients ont subi une vénographie bilatérale avant l'opération et 10 jours après. Huit patients (16%) ont développé une thrombose veineuse dans le groupe de contrôle, contre 1 (2%) dans le groupe traité (p = 0.015, 95% CI 0.02–0.67). Trois embolies pulmonaires sont survenues dans le groupe de contrôle et 1 dans le groupe traité (p = 0.27 95% CI 0.04–2.44) aucune n'étant fatale. La perte de sang intra-opératoire et post-opératoire n'a pas varié de manière significative entre les deux groupes. Notre étude démontre que l'incidence de la thrombose veineuse profonde post-opératoire chez les patients asiatiques est notable bien qu'elle soit moindre que dans les pays occidentaux et confirme la sûreté et l'efficacité du calcium nadroparine pour la prévenir aprés un remplacement total de la hanche.*

Reprint requests to: Y. C. Yoo

Introduction

Traditionally, in Asia, the risk of deep vein thrombosis (DVT) following orthopaedic surgery to the lower limb, has been considered low, and heparin or low molecular weight heparin (LMWH) is not routinely used for thromboprophylaxis [2]. Recent studies in Korea [4] and Malaysia [2] show that the incidence of DVT following surgery to the hip and knee in the absence of thromboprophylactic measures is approaching that in Western populations. This prompted us to study the efficacy of a LMWH in preventing DVT in Korean patients undergoing elective total hip replacement. Previous studies have shown LMWH to be effective in preventing DVT and, in particular, proximal deep vein thrombosis in such patients [3, 6, 7, 10].

Patients and methods

An open, prospective, comparative randomized trial was carried out in 4 Korean University Hospital Medical Centres, over a period of one year (September 1994 – September 1995). A total of 100 patients were randomized into a treatment group (50 patients) and a control group (50 patients). The control group did not receive unfractionated heparin or any other anticoagulant; it is not the clinical practice in Korea to prescribe prophylactic anticoagulants to patients undergoing elective total hip replacement.

Men and women aged over 40 years, weighing 40 – 100 kg, undergoing elective uncemented total hip replacement for the first time, and who had given informed consent, were eligible for inclusion. Exclusion criteria were pregnancy, a recent history of thrombo-embolic events, allergy to heparin or LMWH, thrombocytopenia ($< 100{,}000/mm^3$), innate or acquired coagulation deficiency, and contraindications to phlebography. Patients undergoing repeat, or non-elective hip surgery, were not included in the study.

Nadroparin calcium (Fraxipoarine Sanofi, Winthrop, France) is an LMWH with a mean molecular weight of 4,500 Daltons. Nadroparin calcium was supplied as a concentrated solution containing 10,400 aXa IU/ml in pre-filled syringes. Syringes were supplied in 3 sizes: – 0.3 ml, 0.4 ml and 0.6 ml. The first subcutaneous injection was given 12 h prior to surgery, the second 12 hours after completion of surgery, and subsequent injections once daily in the morning. The initial dose was 41 IU/kg up to and including the third day after operation. From the 4th to the 10th days after operation the dosage was increased to 62 IU/kg per single subcutaneous injection. This regime is similar to that used by Leyvraz et al. [7], and is the dose recommended by the manufacturer.

For the duration of the trial, aspirin and aspirin containing compounds, anti-platelet agents, non-steroidal anti-inflammatory drugs, unfractionated heparin, dextran and oral anticoagulants were never given, and support stockings were not used.

The primary abnormality to be sought was DVT at day 10. Deep vein thrombosis was diagnosed by bilateral phlebography which was performed both preoperatively and 10 days after operation. Other data collected were the incidence of pulmonary embolus, and the amount of intraoperative and postoperative bleeding. A ventilation-perfusion scan was performed on patients in whom a DVT was diagnosed.

All patients were examined daily for signs of DVT. The bilateral venogram performed on the 10th day after operation was read, without the clinical records being made available, by an independent radiologist. If a pulmonary embolus was suspected clinically, a ventilation perfusion scan was performed. Intra- and postoperative bleeding was assessed, first according to the clinical impression of the surgeon (recorded as normal, greater than normal, less than normal), and then by recording the blood loss collected by suction, swabs, drainage volume and the number and amount of blood transfusions. Haemoglobin levels, platelet counts and APTT were measured before operation and on the 4th and 10th days after.

Fisher's exact test was used to compare the incidence of DVT, pulmonary embolism and bleeding. All p-values were two tailed. The odds ratio and the relative risk were calculated for DVT together with thrombosis as well as with their corresponding 95% confidence intervals.

For testing differences in the laboratory parameters between treatment groups, the analyses of variance tables based on generalised line models were used. Logistical regression was used to assess which factors may have accounted for variability between risk factors. Breslow-Day statistics were used to examine the homogeneity of results across strata. On the basis of a 30% incidence of DVT in the placebo group, a sample size of 50 in each group with an expected 60% reduction in the incidence of DVT in the treated group, yielded at a 95% level of significance and a power greater than 70%. All statistical procedures were performed using the statistical analysis system (SAS).

Table 1. Distribution of patients by age and treatment

Age (yrs)	Treated group	Control group	Total
≤50	25	17	42
50 – 60	17	23	40
>60	8	10	18
Total	50	50	100
3 – 2.646	$P = 0.266$	df = 2	

Table 2. Distribution of patients by sex and treatment

Statistic	Treatment group	Control group	Total
Females	11	6	17
Males	39	44	83
Total	50	50	100
$Chi^2 - 1.134$	$P = 0.287$	df = 1	

Table 3. Distribution of patients by history of risk factor and treatment

Risk Factor	Treatment group	Control group	*P*-value
Smoking	23	31	0.16
Obesity	6	3	0.485
Thromboembolic Event	0	0	–
Malignancies	1	2	0.500*
Immobilization	1	1	–

* Fisher's exact probability

Results

The baseline characteristics were similar in both groups (Tables 1–3). There was 1 case of proximal DVT in the nadroparin group (2%), and 8, of which 3 were proximal, in the control group (16%). Only 1 DVT occurred in patients less than 50 years of age. None of the patients had clinical symptoms of DVT (Table 4). In the nadroparin group 1 patient developed a non-fatal pulmonary embolism, compared to 3 patients in the control group, the diagnosis being confirmed by ventilation/perfusion scans. The intraoperative blood loss, whether judged clinically or according to aspirated volume, was similar in both groups. However, the mean volume of intraoperative blood transfusion was slightly greater in the nadroparin group, although the number of patients receiving a transfusion was similar. Drainage after operation and

Table 4. Radiographic results after treatment period of 10 days

	Treatment group	Control group	*P*-value	Relative risk	95% Cl
DVT	1	8	0.015*	0.13	(0.02, 0.67)*
Proximal	1	3	0.270	0.30	(0.04, 2.44)
Distal	0	5	0.025		
P. E. cases	1	3	0.270	0.30	(0.04, 2.44)

* Significant
P. E.: pulmonary embolism

Table 5. Distribution of patients by bleeding severity and treatment

Evaluation day	Bleeding severity	Treated group	Control group	*P*-value
D0 (surgery)	Normal/less	43	47	0.317
	More	7	3	
D1 (first 24 h)	Normal/less	45	49	0.207
	More	5	1	
D2–D9	Normal/less	45	48	0.655
	More	4	2	
D10 (end)	Normal/less	24	25	–
	More	1	0	

Table 6. Change of laboratory findings by treatment

		Treatment	Control
Number		50	50
Hb (mean g/100 ml)	Entry	13.09	13.45
	D10	11.45	11.92
Platelets (mm 3×103)	Entry	304	271
	D10	388	335
APTT (s)	Entry	25.5	26.6
	D10		25.3625.9

the volume of blood transfusion were similar in both groups. There were no cases of deep wound haematoma and no patient required reoperation (Table 5). As expected, the use of nadroparin did not result in any increase in the APTT. Haemoglobin levels on day 10 were similar in both groups, as were platelet counts. No cases of thrombocytopenia (platelets $<100{,}000$) were noted (Table 6).

Discussion

Whilst venous thromboembolism is known to be a common complication of hip replacement surgery in Western countries [10], it has been considered rare in Asia. In Singapore, Mitra et al. found an incidence of only 9.7% in a series of 72 patients who underwent unilateral phlebography following surgery for hip fracture [8]. In Korea, Kim et al. [4] reported in 1996 that the incidence of DVT after total hip arthroplasty was as high as 20% whereas in 1988 they had reported a low incidence of DVT [5]. In Malaysia, Dhillon et al. [2] suggest that postoperative DVT in Asia is increasing, since they recorded an incidence of 64.3% after total hip replacement and 76.5% after total hip and knee replacement. Further indirect evidence for an increasing incidence of DVT in Asia comes from a 15 year retrospective analysis of autopsy records in Hong Kong, where the incidence of pulmonary embolus increased from 1.08% in the first 5-year period to 2.77% in the last 5-year period [1].

While the incidence of DVT in the placebo group is less than the 51% recorded in the placebo group in a Canadian study [14], it still represents a considerable degree of morbidity. Proximal DVT was relatively frequent and accounted for 33% of all incidents. In our study the ratio of proximal to calf DVT in the placebo group was 1 : 1.6. By contrast, in European and North American studies the ratio was 1 : 4 in patients receiving LMWH prophylaxis [3, 7].

Nadroparin thromboprophylaxis reduced the incidence of DVT by 87%. A smaller but still large reduction was noted by Turpie et al. [11] in their

placebo-controlled LMWH thromboprophylaxis study in patients undergoing elective hip replacement. This major decrease in DVT was not associated with an increased risk of bleeding, one risk which many surgeons consider when deciding not to use heparin thromboprophylaxis [9].

Conclusion

The incidence of DVT in Asian patients undergoing elective total hip surgery is sufficient to warrant the use of thromboprophylactic measures. Our study confirms previous reports [3, 6, 7, 10] that a once-daily weight adjusted dose of LMWH is an effective and well-tolerated method of thromboprophylaxis for such patients.

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