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THE JOURNAL OF BONE & JOINT SURGERY (BRITISH)

Prevention of deep-vein thrombosis after total knee replacement

RANDOMISED COMPARISON BETWEEN A LOW-MOLECULAR-WEIGHT HEPARIN (NADROPARIN) AND MECHANICAL PROPHYLAXIS WITH A FOOT-PUMP SYSTEM

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The optimal regime of antithrombotic prophylaxis for patients undergoing total knee arthroplasty (TKA) has not been established. Many surgeons employ intermittent pneumatic compression while others use low-molecular-weight heparins (LMWH) which were primarily developed for total hip arthroplasty. We compared the efficacy and safety of these two techniques in a randomised study with blinded assessment of the endpoint by phlebography.

We randomised 130 patients, scheduled for elective TKA, to receive one daily subcutaneous injection of nadroparin calcium (dosage adapted to body-weight) or continuous intermittent pneumatic compression of the foot by means of the arteriovenous impulse system.

A total of 108 patients (60 in the LMWH group and 48 in the mechanical prophylaxis group) had phlebography eight to 12 days after surgery. Of the 47 with deep-vein thrombosis, 16 had received LMWH (26.7%, 95% CI 16.1 to 39.7) and 31, mechanical prophylaxis (64.6%, 95% CI 49.5 to 77.8). The difference between the two groups was highly significant ($p < 0.001$). Only one patient in the LMWH group had severe bleeding.

We conclude that one daily subcutaneous injection of calcium nadroparin in a fixed, weight-adjusted dosage scheme is superior to intermittent pneumatic compression of the foot for thromboprophylaxis after TKA. The LMWH scheme was also safe.

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Total knee arthroplasty (TKA) is associated with a substantial risk of developing deep-vein thrombosis (DVT) and pulmonary embolism (PE).[1-3] Venous stasis,[4,5] injury to the vascular endothelium, and release of tissue thromboplastin are all significant in the development of venous thrombosis and commonly occur during and after TKA.[6-8] The reported incidence of total DVT after TKA without prophylaxis is between 40% and 84%, with a prevalence of proximal DVT which has a higher potential to cause PE, of from 9% to 20%.[9-12] The late sequelae of DVT may also represent a clinical problem, since 50% to 60% of patients with symptomatic proximal vein thrombosis and 30% of those with symptomatic calf vein thrombosis[13] develop chronic venous insufficiency.

Several types of thromboprophylaxis have been recommended for patients undergoing TKA,[10,13-16] including antiplatelet drugs,[17] intermittent pneumatic compression of the leg,[18-21] standard or adjusted low-dose heparin,[22,23] oral anticoagulants[17] and, more recently, low-molecular-weight heparin (LMWH),[10,13,14,24,25] which appears to be the most effective prophylactic agent. Most studies on LMWH have been performed on patients undergoing total hip replacement (THR).[24-28] These drugs also significantly decrease the incidence of DVT after TKA but, like all anticoagulants, they carry a small but real risk of postoperative bleeding (1% to 5%).[29-33] Recently, a meta-analysis has suggested that LMWH is more effective than warfarin, low-dose heparin or a placebo in this setting.[34]

Since the skin cover is thin over the knee, haematomata and haemarthroses may lead to problems of wound healing, skin necrosis, infection and stiffness of the joint, thereby compromising the functional result of the TKA. Mechanical prophylaxis may avoid or decrease these complications but the classical whole-leg intermittent compression boots are not suited to knee surgery. In 1983, Gardner and Fox[35] showed that external activation by a venous foot pump after surgery reduced venous stasis and may prevent venous thrombosis. Based on this principle, the arteriovenous impulse system foot pump (AVIS) was developed, and a few studies have suggested that it can decrease the incidence of DVT after THR,[36-38] hemiarthroplasty for hip fractures,[39] and TKA.[40,41] In healthy volunteers, the device induced an increase in the peak velocity and flow of venous blood in the common femoral

vein similar to that produced by whole-leg compression boots.[42]

Our aim was to compare the efficacy, as judged by the incidence of DVT on phlebography, and the safety, i.e., the incidence of bleeding, of a LMWH (calcium nadroparin, Fraxiparine; Sanofi-Winthrop, Gentilly, France) and mechanical prophylaxis (AVIS) in patients undergoing unilateral TKA.

Patients and Methods

Between October 1995 and September 1997, 308 patients underwent primary TKA in our two centres. Table I shows the reasons for exclusion of 178 of these patients from the study leaving 130 aged 40 years or more and weighing between 40 and 100 kg who participated. Randomisation was achieved using a casual figures table, along with sequentially numbered sealed envelopes in each centre. The protocol of the study was approved by the Ethics Committees in the two institutions and all patients signed written informed consent forms.

The 130 eligible patients (99 women and 31 men) were randomly assigned to receive one daily subcutaneous injection of LMWH (67 patients) or to mechanical prophylaxis (63 patients). Bilateral phlebography was obtained in 108 (83%) patients, while 15 were assessed only by venous compression ultrasonography, either because phlebography was technically not possible or was refused by the patient. Thus, objective DVT screening was carried out in 64 patients who had LMWH and 59 with mechanical prophylaxis. The difference of 2% between these two proportions was not statistically different.

The clinical details, surgical characteristics and baseline risk factors were similar in the two groups (Table II).

All prostheses were cemented, posterior stabilised knees (Insall-Burnstein; Zimmer, Warsaw, Indiana or Wallaby II; Sulzer Medica, Winterthur, Switzerland) with patellar resurfacing. Before inflation of the tourniquet, the leg was exsanguinated. Antibiotic prophylaxis, with two doses of a third-generation cephalosporin, was given before and after operation. The type and duration of anaesthesia were recorded. Postoperative treatment included bed rest with physiotherapy for two days, followed by active mobilisation and full weight-bearing.

Table I. Reasons for exclusion or non-inclusion of 178 of the 308 consecutive patients who had TKA

Reasons for exclusion or non-inclusion	Number of patients
Refusal to sign the informed consent form	40
History of DVT or PE in the last six months	38
Contraindication to phlebography	20
Weight >100 kg or <40 kg	16
Revision of TKA	13
Prosthesis preserving the posterior cruciate ligament	11
Skin lesions on the foot	8
Severe arterial hypertension	8
History of cerebrovascular accident	6
Bilateral TKA	3
Contraindication to anticoagulation	4
Severe chronic renal insufficiency	2
Known bleeding disorder	2
Severe hepatic insufficiency	1
Postponed surgery	6
Active DVT at inclusion	0
Total	178

Antithrombotic prophylaxis. A total of 67 patients received calcium nadroparin which was injected subcutaneously 12 hours before and 12 hours after surgery, then once daily for ten to 12 days. The daily doses were adjusted to the patient's body-weight (<50 kg, 2850 Axa IU; 51 to 70 kg, 3800 Axa IU; 71 to 100 kg, 5700 Axa IU). The remaining 63 patients were treated with AVIS (Novomedix, Andover, UK) without chemoprophylaxis or additional

Table II. Details* of the 130 patients included in the study

Characteristics	Method of antithrombotic prophylaxis	
	LMWH	Mechanical
Number of patients	67	63
Gender (male:female)	20:47	11:52
Mean age in years (range)	74 (43 to 86)	72 (49 to 88)
Mean body mass index (range)	43.6 (32.2 to 57.7)	44.7 (32.7 to 58.8)
Number of patients with:		
Osteoarthritis	59	62
Rheumatoid arthritis	6	3
Arterial hypertension	28	28
Diabetes mellitus	4	4
Varicose veins	14	12
Previous history of DVT or PE	2	3
Active neoplasm	4	2
Cardiac insufficiency	2	4
Type of anaesthesia (general:spinal)	26:41	32:31
Duration in minutes of (range):		
Anaesthesia	195 (130 to 300)	190 (120 to 290)
Operation	140 (80 to 225)	130 (70 to 230)
Tourniquet	80 (60 to 120)	71 (50 to 135)

* intergroup differences were not significant for all items

Table III. Grading system used for evaluation of haematoma and haemarthrosis

Description	Grade
No haematoma, no haemarthrosis	I
Minor haematoma around the wound without haemarthrosis	II
Moderate haematoma around the wound extending to the calf, thigh or popliteal region with or without moderate haemarthrosis. No rehabilitation restriction	III
Important haematoma with significant haemarthrosis threatening wound healing and causing delay in the rehabilitation programme and requiring a knee aspiration	IV
Surgical haematoma or haemarthrosis with mandatory reoperation because of wound necrosis or nerve compression	V

elastic stockings. The device consists of an electrically-driven air compressor with an air reservoir which delivers intermittent pneumatic impulses by a small pad, shaped to flatten the plantar arch. The compressor rapidly inflates the pad (0.4 s) and then deflates it after one second. This cycle was repeated every 20 seconds. The device was applied to both legs 12 hours before surgery, discontinued during the operation, and then reapplied after it. It functioned at all times except during walking and physiotherapy. The duration of use was recorded daily until phlebography was undertaken. Patients who discontinued mechanical prophylaxis were given the LMWH regimen in use in each institution.

In both groups, thromboprophylaxis with acenocoumarol was begun after the phlebographic control and continued for about six to eight weeks after discharge from hospital, according to the usual practice in the two centres.

Assessment of thromboembolic events. The overall incidence of DVT was assessed by bilateral phlebography[12] eight to 12 days after TKA, or earlier if symptoms suggesting DVT or PE occurred. When phlebography was impossible, venous compression ultrasonography was carried out, with incompressibility of the vein being diagnostic for DVT.[43] At the end of the study, all venograms were reviewed by two expert, independent, radiologists from the participating centres and conflicting assessments were adjudicated by a third expert. DVT was classified according to the localisation (operated or non-operated leg), extent (large thrombi >5 cm; small thrombi <5 cm), and anatomical site (calf, popliteal, femoral or iliac). All thrombi located at or extending into or above the popliteal veins were classified as proximal.

Bleeding. Intraoperative blood loss was determined by recording the amount of blood collected in the suction system, by weighing all the surgical gauze and by estimating the volume of blood lost in the drapes. Postoperative bleeding was assessed by recording the volume of blood transfused while in hospital and the amount collected in the closed-drainage system. The haemoglobin and haematocrit values were recorded preoperatively and on one, three, six and ten days after surgery.[43] The presence of a haematoma and/or a haemarthrosis at the site of operation was assessed by clinical examination on the second, fourth, sixth, eighth and tenth days after surgery.

The extent of haematoma and/or haemarthrosis at the knee was assessed using a five-grade scale (Table III). At the end of the study, a haematoma and/or haemarthrosis index (HH index) was determined.

Study endpoints. We used combined total phlebographically-proven DVT and/or clinically suspected and objectively confirmed PE and surgical haematoma and/or haemarthrosis requiring operation (grade V) as primary endpoints for the study. The extent (large/small) and location of thrombi (proximal/distal) as well as total blood loss and changes in haemoglobin and haematocrit were secondary endpoints. All patients were examined clinically between two and three months after discharge from hospital to detect late DVT or PE, post-thrombotic syndrome complications at the site of operation and other adverse events. The functional outcome was also assessed.

Data were analysed on an intention-to-treat basis; all patients with and without phlebography were included. Intergroup comparisons were determined using either the chi-squared or Student's *t*-test with significance set at $p < 0.05$. All other p values were considered not significant. The 95% confidence intervals (95% CI) were determined using the confidence interval analysis software program (*BMJ*, London, UK).

Results

Thromboembolic events. DVT was diagnosed in 47 of the 108 patients who had phlebography. In addition, three of the 22 who did not have this investigation had DVT diagnosed by venous compression ultrasonography.

In an intention-to-treat analysis the frequency of DVT was 23.9% (95% CI 14.3 to 35.9) and 54.0% (95% CI 40.9 to 66.6) in the LMWH group and in the mechanical prophylaxis group, respectively. The difference is statistically significant ($p < 0.01$). When the analysis was restricted to the 108 patients who had phlebography, 47 had proven DVT with 16 out of 60 in the LMWH group (26.7%, 95% CI 16.1 to 39.7) and 31 out of 48 in the group given mechanical prophylaxis (64.6%, 95% CI 49.5 to 77.8). Again, the difference was statistically significant ($p < 0.001$). There was no statistically significant difference between the two regimens with respect to proximal DVT. The prevalence of DVT along with the location and extent in the 130 eligible patients is given in Table IV. Only one patient, in the mechanical group, had clinical symptoms of DVT, which was confirmed by phlebography five days after surgery. All other DVTs were asymptomatic. No patient

Table IV. The prevalence, location and extent of DVT for the 67 patients who received LMWH and the 63 given mechanical prophylaxis, by number, *percentage* and 95% CI

	Method of antithrombotic prophylaxis		
	LMWH	**Mechanical**	**p value**
Total	16 (*23.9*; 14.3 to 35.9)	34 (*54.0*; 40.9 to 66.6)	<0.01
Distal	14 (*20.9*; 11.9 to 32.6)	30 (*47.6*; 34.9 to 60.6)	<0.005
Proximal	2 (*3.0*; 0.4 to 10.4)	4 (*6.3*; 1.7 to 15.5)	0.4
Operated leg	13 (*19.4*; 10.8 to 30.9)	28 (*44.4*; 31.9 to 57.5)	<0.005
Bilateral	0	2 (*3.2*; 0.4 to 11.0)	0.2
Large	9 (*13.4*; 6.3 to 24.0)	20 (*31.7*; 20.6 to 44.7)	<0.01
Small	7 (*10.4*; 4.3 to 20.3)	14 (*22.2*; 12.7 to 34.5)	0.07

Table V. Blood loss and need for transfusion during the study period*

	Method of antithrombotic prophylaxis	
	LMWH (n = 63)	**Mechanical (n = 56)**
Median blood loss in ml (range)		
Intraoperative	500 (80 to 1600)	480 (100 to 1780)
Postoperative	640 (40 to 2180)	600 (0 to 1570)
Total blood transfused (ml; range)	1080 (0 to 5510)	1000 (0 to 2800)

* blood loss was not recorded in four patients who had LMWH and in seven given mechanical prophylaxis

Table VI. Bleeding evaluation in the operated knee*

	Median size of haematoma as mean HH† index (range)	
Days after surgery	**LMWH (n = 62)**	**Mechanical (n = 54)**
2	2 (1 to 5)	2 (1 to 4)
4	2 (1 to 5)	2 (1 to 4)
6	2 (1 to 5)	2 (1 to 3)
8	2 (1 to 4)	3 (1 to 4)
10	2 (1 to 4)	2 (1 to 4)

* local evaluation was not recorded adequately in five patients who had LMWH and in seven who had mechanical prophylaxis
† haematoma and/or haemarthrosis index (see text)

had clinical signs or symptoms of PE and no deaths were recorded during the study period.

Bleeding. Intraoperative and postoperative blood loss, as well as the total amount of blood transfused, are summarised in Table V. The mean decrease in the haemoglobin level between the day before operation and the tenth day after was 17.4 g/l (CI 95% 14.4 to 20.4) and 16.0 g/l (CI 95% 12.8 to 19.2) in the groups given LMWH and mechanical prophylaxis, respectively. None of these differences reached statistical significance. One patient receiving LMWH (1.5%, 95% CI 0.04 to 8.3), presented with a major bleeding complication (grade V) at the operative site in the immediate postoperative period. This required a blood transfusion of 5510 ml but further operation was not undertaken. Overall, the daily mean HH index did not differ significantly between the two groups (Table VI). No patient in the mechanical group had a bleeding complication.

Other adverse reactions. The impulse system was worn for a mean of 22 hours (7 to 24) each day. Sixteen patients (25%) discontinued wearing the device because of substantial discomfort, including noise, heat from the slipper, and sleeplessness. None developed skin lesions caused by the slipper. No adverse reactions were noticed in patients given LMWH and there was no significant difference in the platelet count between the two groups (data not shown).

Follow-up. Two to three months after hospital discharge all wounds had healed without significant differences between the two groups. No patient had symptoms of late DVT or PE after hospital discharge.

The mean knee flexion on the tenth day after operation was 70° (45 to 100) in the LMWH group and 70° (45 to 95) in those who had mechanical prophylaxis (p = 0.18). At follow-up, the mean corresponding ranges of movement were 100° (85 to 125) and 100° (75 to 130) (p = 0.5).

Discussion

Our results confirm that thromboembolic complications are an important problem after TKA. Although all patients received some form of prophylaxis, half of them had a phlebographically-proven DVT on the tenth postoperative day. This prevalence was related to the type of prophylaxis used; only about 25% of patients given LMWH had DVT compared with 65% of those who had mechanical prophylaxis. Thus, the AVIS, which is theoretically attractive to many surgeons, did not confirm its preliminary, promising results.[40,41]

Wilson et al[40] compared the incidence of DVT in 28 patients treated postoperatively with AVIS and 32 patients without prophylaxis after TKA in a prospective, randomised controlled study. The phlebograms, which were obtained on the side of operation only, showed no significant difference in the overall incidence of DVT (69% in patients without prophylaxis compared with 50% in patients with AVIS) but a significant decrease in the incidence of proximal and major DVT in the group of patients treated by the mechanical device. In contrast, Westrich and

Sculco[41] carried out a prospective, randomised study in 122 patients undergoing TKA to assess the efficacy of pneumatic plantar compression combined with aspirin compared with aspirin alone after TKA. They showed a significant decrease in the occurrence of DVT in those treated by pneumatic plantar compression and aspirin (prevalence of DVT, 27%) compared with patients given aspirin alone (59%). They also described a significant decrease in the incidence of proximal and major DVT in patients with mechanical prophylaxis. These studies, however, included relatively few patients, the efficacy was assessed by unilateral phlebograms in a subset of patients, and the control group was not given the optimal prophylactic regimen. In these two trials, and also in our study, elastic stockings were not applied to the patients in addition to the intermittent compression, as is now recommended by the manufacturer.[40]

One potential advantage of mechanical prevention, a lower incidence of troublesome bleeding, was less important than anticipated since only one case of major bleeding was registered in our study, and occurred in the LMWH group (incidence of major bleeding 1.5%, 95% CI 0.04 to 8.3). The 95% CI, however, is quite large and its upper limit does not exclude the possibility of a higher frequency of severe bleeding.

Mechanical prophylaxis was discontinued in 25% of patients because of discomfort. Manual handling of the foot pump is cumbersome but once-daily subcutaneous injection of a LMWH is much easier to administer.

We recognise that our study has limitations. The sample size was relatively small, although it is one of the largest trials carried out for TKA. It could not be double-blinded, but the main endpoint, phlebographic DVT, was assessed in a blinded fashion by expert radiologists who were unaware of the assigned prophylactic regimen. We showed only that total DVT was diminished, not the clinically more relevant proximal thromboses or PE. Large thrombi of more than 5 cm in length were significantly less frequent ($p < 0.01$) in patients given LMWH than in those who had mechanical prophylaxis. DVT was asymptomatic in all but one patient and it could be argued that such events may not have any clinical relevance but eradication of DVT would ultimately result in a reduction of non-fatal and fatal PE.

Subcutaneous injection of the LMWH nadroparin once a day is superior to the foot intermittent compression system (AVIS) for thromboprophylaxis after TKA. Nevertheless, 26% of patients still had a DVT as demonstrated by phlebography ten days after elective surgery.

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