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Papers

Thromboembolic prophylaxis in orthopaedic trauma patients: a comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium)

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In a prospective, randomized multicentre trial the safety and efficacy of two regimens of a low molecular weight heparin (nadroparin calcium) were compared for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in orthopaedic trauma patients. Two hundred and eighty-three patients with a spinal fracture, a pelvic fracture, or a lower limb injury were randomized to receive either a fixed dose (7500 anti-Xa IC units = 3075 anti-Xa IU) or a variable dose depending on body weight and time since operation (100 to 150 anti-Xa IC units/kg ≅ 40 to 60 anti-Xa IU/kg). The patients continued the prophylactic regimen for 6 weeks, but were withdrawn from the study medication in the presence of a major complication or if they were completely cured from their injury. To assess the rate of DVT, a B-mode ultrasound scan of both legs was performed. Positive results were confirmed by phlebography. If signs or symptoms of PE were present, a ventilation-perfusion scan was performed. Both prophylactic regimens were equally safe. In each group, five patients developed major haemorrhagic complications. In each group, one case of reversible thrombocytopenia was seen. DVT was confirmed by phlebography in one patient given the fixed dose and in four patients given the variable dose. PE was confirmed by ventilation-perfusion scans in one patient with the fixed dose and in two patients with the variable dose. An intention-to-treat analysis was performed on the overall randomized population, with the assumption that all patients who were lost to follow-up had DVT. A therapeutic efficacy analysis was performed on those patients, who completed the course of the prophylactic regimen and in whom B-mode ultrasound scanning was performed 10 days and also 6 weeks after injury. These two modes of analysis showed no significant differences in the incidence of DVT or PE between both prophylactic regimens. In conclusion, both regimens were equally safe following a spinal fracture, a pelvic fracture or a lower limb injury. The risk of DVT and PE was similar with both regimens. Copyright © 1996 Elsevier Science Ltd.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) remain a major cause of morbidity and mortality in injured patients. The reported incidence varies widely: 20–90 per cent for DVT and 4–22 per cent for PE as reported in three recent reviews[1–3]. Although these statistics strongly support thromboembolic prophylaxis in injured patients, there is little literature documenting the efficacy and safety of low molecular weight heparin (LMWH).

In 1993 Kujath et al.[4] reported that a single daily subcutaneous injection of the LMWH, nadroparin calcium (Fraxiparine®, Sanofi, Paris, France) is safe and effective in preventing DVT in patients with an injury of the leg. In this prospective study, the authors evaluated 253 injured patients who required immobilization with a plaster cast because of leg injuries. The patients were randomized to receive either a fixed dose of nadroparin calcium (3075 IU = 0.3 ml) subcutaneously once a day, or no prophylaxis. The incidence of DVT was 16.5 per cent in the untreated group and 4.8 per cent in the nadroparin calcium group, representing a statistically significant reduction of the thromboembolic events ($P < 0.01$). There were no major haemorrhagic complications.

On the other hand, in elective orthopaedic surgery, extensive investigations have shown the efficacy and safety of subcutaneous LMWH in preventing DVT in high-risk patients[5–8]. In a prospective study of the prevention of DVT after elective total hip replacement, Leyvraz et al.[9] also administered the LMWH nadroparin calcium once a day, but individually adjusted the dose according to body weight and time since the operation. The total incidence of DVT in patients receiving LMWH prophylaxis was 12.6 per cent and there was only one major haemorrhagic complication (0.51 per cent).

These encouraging results, indicating efficacy and safety with once-daily administration, prompted us

to compare the two prophylactic LMWH regimens (fixed dose and body-weight-adjusted dose) for the prevention of DVT after spinal, pelvic or lower limb injuries.

The aim of the present study was to compare the thromboprophylactic effects and haemorrhagic complications of one single daily injection of LMWH, Fraxiparine®, administered either as a fixed dose (3075 IU) or as an individualized dose according to bodyweight and time scale surgery (40 IU/kg till day 3 and 60 IU/kg from day 4).

Patients and Methods

Study design

The study was designed as a prospective, randomized, open multicentre trial. Between 13 March 1991 and 7 January 1993, adult patients with orthopaedic injuries were randomly assigned to a fixed LMWH dose (group A) or a dose adjusted according to body weight and time since surgery (group B).

Inclusion criteria

Patients were included if they were older than 18, if their body weight was between 45 and 100 kg, had a spinal or pelvic fracture or a lower limb injury, and had an expected postoperative stay in hospital of at least 8 days.

Patients had to give their informed consent before entering the study.

Exclusion criteria

Patients were not included in the presence of one of the following items: age <18 years; bodyweight <45 kg or >100 kg; history of impaired hepatic function; history of impaired renal function; pregnancy; known bleeding diathesis; treatment with anticoagulants or antiplatelet drugs; multiply injured patient with more than five injuries; admission to the clinic >8 h after injury; operative procedures planned for >5 days after hospital admission.

Low molecular weight heparin (LMWH)

A single batch of the LMWH nadroparin calcium (Fraxiparine®, Sanofi, Paris, France) was used. It had an anti-factor II (anti-IIa) specific activity of 27 IU (tested against the 4th International Heparin Standard) and an anti-factor Xa (anti-Xa) activity of 89 IU/mg when compared with the international standard for LMWH. It was supplied as a concentrated solution containing 10250 anti-Xa IU/ml, in prefilled syringes of 0.3 ml (3075 IU) and 0.6 ml (6150 IU).

Prophylactic regimens

The study was performed as an open trial, comparing two randomized prophylactic groups, one receiving a fixed LMWH dose and the other an individualized dose. The prophylactic treatment groups are further named: group A (fixed dose of 0.3 ml=3075 IU nadroparin calcium subcutaneously once a day), and group B (individualized dose of nadroparin calcium subcutaneously once a day, adjusted for body weight and time since surgery: *Table I*). Injections were given subcutaneously once a day in the lateral part of the thigh or in the abdominal wall.

Table I. Dose of nadroparin calcium given as a once-daily subcutaneous injection to patients in group B; the dose was adjusted according to the patient's weight and the time elapsed since operation

	Dose (ICU/ml)	
Body weight (kg)	*From injury to day 3 after operation*	*From day 4 after operation*
<50	5000 (= 0.2 ml)	7500 (= 0.3 ml)
50 to 70	7500 (= 0.3 ml)	10000 (= 0.4 ml)
>70	10000 (= 0.4 ml)	15000 (= 0.6 ml)

No placebo group was included for ethical reasons. In both groups, the first injection was given within 8 h of injury, and subsequent injections on each morning of the following days. In group B, the increase in dosage was incorporated into the study protocol because of earlier observations that higher doses of unfractionated heparin were needed in the later postoperative period to maintain the APTT in the desired range[9].

Patients continued the prophylactic regimen for 6 weeks, but were withdrawn from the study if there was a major complication or if the treatment of the injury was complete.

Diagnostic procedures/assessment of thromboembolism

Screening for DVT was done 10 days and 6 weeks after the injury, or earlier if the initial injury was cured. This was done with either bilateral B-mode duplex ultrasound scanning or bilateral impedance rheoplethysmography. Patients with positive findings or equivocal findings underwent a bilateral ascending phlebography. Clinically suspected DVT had to be confirmed by bilateral ascending phlebography.

Clinically suspected pulmonary embolism had to be confirmed by lung ventilation-perfusion scanning or angiography.

Recording of complications

Throughout their hospital stay, the patients were examined daily for wound and injection-site haematomas as well as bleeding elsewhere. During the study, patients were assessed for any haemorrhagic complications.

Bleeding was considered major if there was a wound haematoma necessitating surgical intervention, macroscopic haematuria, gastrointestinal bleeding, or any bleeding requiring blood transfusion and/or interruption of trial medication. Haematological parameters (Hb, Hct and platelets) were determined before randomization and on days 5, 10, 15, 20 and 42 after the injury, or when the initial injury was cured.

Statistical methods

Initially we performed an analysis based on 'intention-to-treat', counting all the patients included initially. 'Deep vein thrombosis' status was assigned to patients who for any reason could not be followed up until the end of the trial. Secondarily we

performed an efficacy analysis; this analysis was based on those patients who were treated exactly according to the protocol and in whom the protocol requirements were fully met. The standard statistical tests used for comparing the two treatment groups in each study were the χ^2 test and the Fisher's exact test.

Ethics

The study was approved by the Ethics Committees of all the 29 participating trauma centres. The patients gave their informed consent to participate before entering the study.

Results

Between 13 March 1991 and 7 January 1993, 283 patients were randomized to receive either a fixed subcutaneous dose of 3075 IU nadroparin calcium (group A, $N=142$) or a variable dose of subcutaneous nadroparin calcium depending on body weight and time elapsed since surgery (group B, $N=141$). The study groups were well matched.

No significant difference between the two treatment groups was found for all the demographic parameters (*Table II*).

The characteristics of the injury were also well balanced between the two treatment groups (*Table III*). Almost half of the study population suffered from hip fractures. Two hundred and eight patients had general anaesthesia and 190 patients had undergone an osteosynthesis (*Table IV*).

Although 283 patients were randomized, several of them dropped-out for various reasons (*Table V*). No significant difference was observed between group A and group B.

Finally 215 patients could be included in the efficacy analysis 10 days after randomized and 150 patients 6 weeks after randomization.

Deep vein thrombosis (DVT)

Intention-to-treat analysis According to the intention-to-treat analysis principle, every missing patient

Table II. Clinical characteristics in the two study groups; figures represent numbers of patients unless otherwise stated

	Prophylactic regimen	
Demographic parameters	*Group A (N = 142)*	*Group B (N = 141)*
Age in years (mean ± SD)	61.7 ± 23.1	60.5 ± 22.7
Age distribution		
<40 years	32	34
>40 years	107	107
Not specified	3	0
Bodyweight in kg (mean ± SD)	67.7 ± 12.3	70.0 ± 12.1
Height in cm (mean ± SD)	168 ± 13	169 ± 11
Men	53	64
Women	86	74
Sex not specified	3	3

Table III. Characteristics of injury in the two study groups; figures represent numbers of patients

	Prophylactic regimen	
Characteristics of injury	*Group A (N = 142)*	*Group B (N = 141)*
Type of injury		
Bone lesion	130	132
Soft tissue injury	5	5
Mixed injury	7	4
Single injury/multiple injury	115/27	112/29
Site of injury		
Pelvis	10	13
Hip	72	72
Lower limb	53	56
Spine	7	4
Soft tissue	12	9

Table IV. Types of treatment

	Prophylactic regimen	
Characteristics of treatment	*Group A (N = 142)*	*Group B (N = 141)*
Type of anaesthesia		
Loco-regional	22	15
General	100	108
Not specified	0	1
Surgery		
Endoprosthesis	24	22
Osteosynthesis	93	97
Soft tissue procedure	5	5
None	20	17

Table V. Reasons for exclusion from efficacy analysis

	Day 10 after injury		*Week 6 after injury*	
	Group A	*Group B*	*Group A*	*Group B*
Total number of patients randomized	142	141	142	141
Reason for screening not performed				
Inclusion violation	7	5	7	5
Premature discharge	3	9	3	9
Death	4	2	8	5
Haemorrhage	5	5	5	5
Thrombocytopaenia	1	1	1	1
Prophylaxis discontinued	1	—	1	2
Refusal of screening	15	10	15	10
Lost to follow-up	—	—	26	30
Total number of patients included for efficacy criterion	106	109	76	74

is considered as a failure (DVT). When this method is applied to our data, no difference at 10 days or 6 weeks after injury was observed between the two treatment groups (25.4 per cent (group A) and 24.8 per cent (group B) at 10 days and 47.2 per cent (group A) and 50.4 per cent (group B) at 6 weeks after injury).

Efficacy analysis In the statistical analysis only based on patients treated exactly according to the protocol (efficacy analysis), one DVT was observed in group A (fixed dose) and four in group B (individualized dose). At 10 days and 6 weeks after injury, the percentages of thrombosis were respectively 0 per cent and 1.3 per cent in group A and 2.8 per cent and 5.4 per cent in group B (*Table VI*).

Analysis by the type of initial injury showed that all patients who developed DVT had a hip fracture; it occurred on the side of the hip fracture in two patients and on the contralateral side in two others. In one patient the side was not specified.

Most of the patients who developed DVT were older than 40, although it developed in one patient with a hip fracture who was younger. In addition, no significant difference in the incidence of DVT was found between patients who had received general anaesthesia and those who had received spinal anaesthesia (1.9 per cent and 2.7 per cent respectively).

Pulmonary embolism (PE)

Ventilation-perfusion scanning confirmed the presence of PE in three patients: one from group A and two from group B. Again, this intergroup difference was not statistically significant. One patient from group B died of massive PE. The patients who developed PE had a hip fracture ($N=2$) or a femoral diaphysis fracture ($N=1$).

Tolerance

Bleeding complications Major haemorrhagic complications occurred in five patients in each group. In group A there was one subdural haematoma on day 2, one recurrent epistaxis on day 3, two haematomas at the operation site necessitating reintervention on day 5, and one metrorrhagia on day 8. In group B there was one recurrent epistaxis on day 2, one haemorrhage at the operation site associated with thrombocytopenia on day 3, one stroke on day 4, one gastrointestinal bleeding on day 7, and one life-threatening epistaxis on day 8 (*Table VI*).

Thrombocytopenia One patient in each group developed LMWH-related thrombocytopenia, on day 10 and on day 3 after injury in groups A and B, respectively. The latter patient needed a massive blood transfusion because of severe operation-site wound haemorrhage following treatment of a hip fracture by an endoprosthesis. The patients' platelet counts decreased from $178 \times 10^9/l$ to $50 \times 10^9/l$ and from $206 \times 10^9/l$ to $39 \times 10^9/l$, respectively, but returned to normal after nadroparin calcium was stopped (*Table VI*).

No other side-effects were observed.

Deaths Twelve patients died during the trial period: eight in group A and four in group B. These differences were not statistically significant. In group A, one patient died after a stroke, two died of cancer, two died of pulmonary infection, two died of acute myocardial infarction and in one the cause of death was unknown (no autopsy performed). In group B, one patient died of cardiac failure, one of pulmonary embolism, one of DVT, and one with cancer died of deterioration of general health.

PE cannot be ruled out as the cause of death in the last two patients, nor in the last patient of group A (cause of death unknown).

Discussion

Screening and diagnosis of DVT in patients with orthopaedic injuries is often difficult[1,10,11]. Currently, impedance rheoplethysmography and B-mode duplex ultrasound scanning are considered as standard techniques for screening[12,13], contrast venography being reserved for patients in whom those tests provide equivocal results, or to confirm the diagnosis in patients with a positive result[1,4,10,13–16].

In our trial, we planned a B-mode duplex ultrasound scan or impedance rheoplethysmography on day 10 after injury and also at week 6 after injury. Most other studies looked at the incidence of DVT after a very short period, usually within the first 10 days, but it is clear that a number of patients returning home after an operation are still at significant risk. In 1990 Scurr[17] showed that patients' mobility may decrease when they get home and that many of the risk factors which occur immediately

Table VI. Clinical data and tolerance data

	Day 10 after injury		*Week 6 after injury*	
	Group A	*Group B*	*Group A*	*Group B*
Clinical events in all patients				
Intention-to-treat analysis (DVT was assigned for patients who could not be followed up until the end of the trial for any reason)	36/142 (25.35%)	35/141 (24.82%)	67/142 (47.18%)	71/141 (50.35%)
Clinical events in screened patients				
Efficacy analysis	0/106	3/109	1/76	4/74
Positive phlebogram/performed screenings	(0%)	(2.75%)	(1.32%)	(5.41%)
Tolerance data				
Major haemorrhage	5	5	5	5
Thrombocytopenia	1	1	1	1

after major surgical operations persist for several weeks, so he suggested that DVT prophylaxis should be continued for longer than the hospital stay. This is why, in planning our trial, we decided to assess the incidence of DVT at 6 weeks after the injury also.

Our drop-out data observed after the first assessment at day 10 after the injury are similar to those reported in the literature after a similarly short observation period, but before the end of the final screening at 6 weeks after injury there were a lot of drop-outs. Increasing the length of the observation period obviously increases the likelihood of a higher number of withdrawals. Although this drop-out rate may give an unfair representation of the true incidence of DVT in this orthopaedic injury population, it probably does not invalidate the data presented here. The number of patients not screened at 10 days and at 6 weeks after injury was found to be similar in both prophylactic regimen groups. The reasons for not screening were similar in both groups: premature discharge and refusal to be screened at day 10 and lost to follow-up at 6 weeks after injury. Moreover, the aim of our study was to compare the efficacy and the safety of two regimens of LMWH, and not to determine the true incidence of DVT in a population with orthopaedic injuries.

The incidence of DVT observed in our population is substantially lower than the 20–90 per cent reported in the literature[1–3]. This can be attributed to several different factors. One is the screening test: contrast phlebography is the standard but we did not use it as primary screening because of its potential drawbacks that include iodine allergy, radiation exposure, and the risk of causing phlebitis, and relied instead on bilateral B-mode duplex ultrasound or bilateral impedance rheoplethysmography. A second factor may be the combined use of LMWH (pharmacological prophylaxis) with elastic stockings (non-pharmacological prophylaxis). A third factor may be the very early application of prophylactic measures, which are likely to be more effective, the earlier they are applied[1]; because their beneficial effects are immediate, they are useful for providing early protection in the interim before pharmacological agents become fully effective[15,18]. Moreover, it seems reasonable to start LMWH prophylaxis as soon as possible, provided the haemorrhagic risk allows this (within 8 h after the injury and before the operation).

We identified two factors associated with an increased risk of developing thromboembolic complications: increased age and hip fracture. Several recently published reports support these findings, showing, as we did, a good correlation between the age of patients and the incidence of DVT[1,10,18–20]. Although thromboembolic prophylaxis is generally recommended in these at-risk patients, our results suggest that prophylaxis should also be considered in young and mobile patients with other risk factors for the disease. Many years ago, Coon[21] warned that injured patients were at an increased risk of developing thromboembolic disease, regardless of their age. Elderly patients with an isolated femoral neck fracture are recognized to be at a high risk of DVT and PE[1,22–24]. This higher risk is confirmed by our study: all patients who developed DVT or PE had a fracture of the femur. Moreover, our study confirms that thrombi in patients with fractures are usually bilateral, even in those with unilateral limb injury[1,18,23,25].

In patients undergoing elective total hip replacement or surgery for a fractured hip, there is some evidence that the type of anaesthesia may affect the incidence of DVT and PE. In particular, regional anaesthesia may reduce the risk. In studies of femoral neck fractures[26] and total hip replacement[27], spinal anaesthesia was associated with a lower incidence of DVT than general anaesthesia. In most injured patients receiving thromboembolic LMWH prophylaxis, spinal anaesthesia does not appear to offer significant advantages over general anaesthesia. In our study the type of anaesthesia made no difference to the incidence of DVT and PE.

Despite the difference between the patient populations in the study by Leyvraz et al.[9] and in ours, their reported incidence of bleeding complications (0.51 per cent) is remarkably similar to ours (0.36 per cent). Only two cases of thrombocytopenia occurred in our population; because of the small number of patients developing it, caution is necessary when interpreting the relationship with administration of nadroparin calcium. In group B, one patient developed thrombocytopenia, but this occurred before the LMWH dose was increased, so there is no relation, but this patient had received a massive red blood cell transfusion earlier, suggesting a probable causal relationship.

Conclusions

There was no statistically significant difference in efficacy or tolerability between the two subcutaneous LMWH prophylaxis regimens. Our study showed that nadroparin calcium, administered once a day in a fixed dose, is as effective as a dose adjusted to body weight in the prevention of DVT and PE in injured patients. The incidence of major bleeding complications and of LMWH-induced thrombocytopenia was low in both groups and makes the LMWH easy and safe to use in patients with orthopaedic injuries.

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