Prevention of thromboembolism in 190 hip arthroplasties

Comparison of LMW heparin and placebo

Michael R. Lassen[1], Lars C. Borris[1], Hanne M. Christiansen[1], Kent L. Boll[3]
Søren P. Eiskjær[3], Bent W. Nielsen[3], Peder Schøtt[2], Agnete D. Olsen[2]
Jennifer C. Rodenberg[4] and Ulf Lucht[3]

Prophylactic efficacy and safety of a low molecular weight (LMW) heparin against postoperative thromboembolic complications were investigated in a double-blind, randomized study. Totally, 210 consecutive patients undergoing total hip replacement were allocated to two groups. Patients in the heparin group received 50 IU anti-Xa per kilo body weight of Logiparin™ once daily, and patients in the placebo group received one daily injection of saline. Additional prophylaxis in all the patients was thigh-length compression stockings beginning on the day of the operation. Deep vein thrombosis was diagnosed by bilateral ascending phlebography between Days 8 and 10 after the operation. Twenty patients were excluded from the evaluation. Thirty of 93 patients in the heparin group compared with 45 of 97 patients in the placebo group suffered a thromboembolic complication during the study ($P = 0.02$). The postoperative blood loss and total number of blood transfusions in the heparin group were higher than in the placebo group. However, the observed differences were of no clinical importance. Adverse effects, including bleeding complications and wound hematomas, were observed in 13 heparin patients and 7 placebo patients (NS). One patient in each group died.

Thromboprophylaxis with LMW heparin once daily was safe and more effective than the placebo in patients undergoing total hip replacement.

[1]Departments of Orthopedics and [2]Radiology, Aalborg Hospital, Aalborg, and
[3]Departments of Orthopedics and [4]Radiology, Århus Municipal Hospital, Århus, Denmark
Correspondence: Dr. Michael R. Lassen, The Venous Thrombosis Group, Department of Orthopedics, Aalborg Hospital, Hobrovej, P.O. Box 365, DK-9100 Aalborg, Denmark

We report a controlled, randomized comparison of the antithrombotic efficacy and safety of a LMW heparin versus a placebo in patients undergoing hip arthroplasty.

Patients and methods

The randomized, double-blind comparative trial in hip surgery took place from February to December 1988 at Aalborg Hospital and Århus Municipal Hospital, Denmark. In all, 281 patients aged 40 years or over, scheduled for elective hip replacement, entered the study. Before randomization, 71 patients were excluded according to the following criteria: treatment with plasma expanders or investigational drugs within 4 weeks prior to the operation; impaired renal or hepatic function; uncontrolled hypertension (diastolic pressure > 120 mmHg); hemorrhagic diathesis; pregnancy; confinement to bed; revision arthroplasty; hypersensitivity to radiopaque dye, heparin, bisulfite, or benzyl alcohol; ongoing anticoagulant therapy; and lack of informed consent. Thus, 210 patients were randomized by random numbers: 105 patients were allocated to prophylaxis with heparin and 105 patients with a placebo. The type of anesthesia was decided before randomization according to the routine of the departments of anesthesia. Arthrosis of the hip joint was the most common indication for the operation (88 percent). Surgery was performed using a posterolateral approach. Patients below 60 years received a cementless prosthesis, and those aged 60 years or over received a cemented prosthesis. Patients were mobilized on the fourth postoperative day (see the statistical section).

After randomization, 20 patients (12 patients in the heparin group and 8 in the placebo group) were withdrawn from the statistical analysis as regards thromboembolism. The reasons were lack of phlebography in 10 patients (7 withdrew their consent, 1 died before examination, 1 developed severe liver dysfunction, and the operation was

cancelled in the last patient) and inconclusive phlebography in the other 10 due to technical difficulties that resulted in a unilateral examination only. Thus, 190 patients completed the study: 93 received heparin and 97 received a placebo. The groups were well matched in terms of baseline characteristics and risk factors (Table 1).

Table 1. Baseline characteristics and risk factors in 190 patients completing the study

	Heparin (n 93)	Placebo (n 97)
Sex (M/F)	45/48	47/50
Age (yr)[a]	67 (40–85)	67 (40–86)
Weight (kg)[a]	73 (40–101)	74 (48–126)
Height (cm)[a]	167 (148–190)	169 (153–194)
Duration of operation (min)[a]	117 (55–200)	123 (50–250)
Anesthesia general/regional[b]	67/26	67/30
Type of prosthesis cemented/noncem.	61/30	69/30
Risk factors		
Varicose veins or leg ulcers	32	28
Previous thromboemb.	6	6
Previous lower limb fracture	13	13
Malignant disease	3	4

[a] Median (range).
[b] Epidural, spinal, or combined epidural/spinal anesthesia.

The heparin

Logiparin™ (Novo-Nordisk, Denmark) is a LMW heparin prepared by controlled enzymatic depolymerization of porcine heparin by heparinase derived from *Flavobacterium heparinum*. The median molecular weight was 4,900, the anti-Xa activity 89 IU/mg, and the APTT activity 47 IU/mg. The preparations contained 10,000 IU anti-Xa/mL.

Prophylactic regimens

Heparin group: 50 units anti-Xa per kg body weight of Logiparin™ injected once daily. Placebo group: isotonic saline injected once daily.

Injections were given subcutaneously in the abdominal wall, and were started 2 h preoperatively and continued for 7 days. Basic prophylaxis in both groups was thigh-length graded compression stockings (TED anti-embolism stockings, Kendall Co). The stockings were applied to both legs 1 h before the operation, and were used day and night until the phlebography. During the operation the stocking on the operated on side was pulled down to below the knee level.

Diagnosis of thromboembolic complications

Bilateral ascending phlebography was carried out postoperatively between Days 8 and 10, or earlier if DVT was suspected. All the examinations started on the operated on side, and were performed by using the method described by Rabinov and Paulin (1972). The contrast medium used was Ihexol® (Omnipaque 240, Nyegaard & Co A/S, Oslo, Norway). All the venograms were evaluated according to Zachrisson and Jansen (1973) by a radiologist who was unaware of the randomization results. If clinical symptoms suggestive of pulmonary embolism (PE) developed, the patient was examined by ventilation/perfusion lung scintimetry. In the case of a positive diagnosis of embolism, the patient was recorded as having a thromboembolic complication, even if the result of the phlebography was normal. When DVT or PE were diagnosed, prophylaxis was discontinued and the patient started treatment with heparin followed by oral anticoagulation for 3 months.

Safety recordings

The clinical course of each patient was followed until discharge from the hospital. Operative blood loss was estimated by the anesthetist. Postoperative blood loss in drains was measured. Repeated measurements of hemoglobin were carried out, starting preoperatively and continuing every second postoperative day. Blood transfusions, formation of hematomas, and reoperations were recorded, as well as adverse effects and local complications at the injection sites.

Statistics

The maximum sample size of 210 patients was determined to achieve a 80–90 percent power of the primary efficacy test, when the relative frequencies of DVT were 0. 12 in the heparin group and 0. 30 in the placebo group.

The study was conducted in three wards. Patients in two of the wards were mobilized on the fourth postoperative day (early) throughout the study. In the third ward, mobilization was routinely delayed until the ninth day; but during the study, it was changed to the fourth day. Due to the obvious differences caused by this change of policy, patients from this ward were retrospectively stratified according to time of mobilization in the efficacy evaluation.

Table 2. Thromboembolic complications in the two groups

		Heparin (n 93)	Placebo (n 97)
	N	n (%)	n (%)
Deep vein thrombosis	73	29 (31)	44 (45)
Pulmonary embolism	2	1 (1)	1 (1)
Thrombus location			
Proximal	59	24 (83)	35 (80)
Distal	14	5 (17)	9 (20)

Proximal = thrombi in the ileo-femoro-popliteal veins.
Distal = thrombi in the crural veins.

Table 3. Distribution of thromboembolism in relation to mobilization policy and prophylaxis

Mobilization	Early (n 162)		Delayed (n 28)	
	Heparin	Placebo	Heparin	Placebo
Thromboembolism absent/present	59/18	47/38	4/12	5/7
Odds for not contracting thromboembolism	3.28	1.24	0.33	0.71
Odds ratio Heparin/placebo	2.65		0.47	
P (Exact) one-tailed	0.003		0.91	

Statistical methods included log-linear analyses of contingency tables, exact test in r by c tables with or without one ordered category, exact test for homogeneity of odds ratios, exact test, and confidence intervals for common odds ratio across several 2 by 2 tables, Wilcoxon two sample rank sum test (Mann-Whitney), binomial test, analysis of variance, repeated measures analysis of variance, weighed analysis of variance, Student's t-test, and Bartlett's test for homogeneity of variance.

Tests concerning risk of thromboembolism, blood losses, and transfusions were one-tailed because the investigator at the protocol stage precluded an increase of risk of thromboembolism and decrease of blood losses and, thus, the need of transfusions caused by heparin treatment. Other tests were two-tailed. All the tests were at the 5 percent significance level; and, accordingly, 95 percent confidence intervals were employed.

Ethics

The patients' consents were obtained after giving information explaining the risks and the potential benefits. The study was submitted to the National Health Service of Denmark and approved by the local ethics committees.

Results

Deep vein thrombosis was diagnosed in 73 patients, (44 were in the operated on leg, 10 in the contralateral leg, and 19 were bilateral). None of these patients developed any clinical symptoms. As described below, pulmonary embolism was diagnosed at autopsy in 1 patient in the heparin group. One patient in the placebo group developed symptoms suggestive of embolism 4 days after the operation, which was verified by a ventilation/perfusion lung scan. Thus, thromboembolism was diagnosed in 75 patients: 30 heparin patients (32 percent), and 45 placebo patients (46 percent; Table 2). The odds of not contracting thromboembolism did not differ in patients who had delayed mobilization ($P = 0.83$, two-tailed, Pearson chi^2 in a log-linear model), whereas the odds were significantly decreased in patients who had early mobilization ($P = 0.0022$, two-tailed, Pearson chi^2 in a log-linear model). The odds ratios for heparin versus placebo were, however, not dependent on time of mobilization ($P = 0.23$, two-tailed, Pearson chi^2 in a log-linear model). The estimated common odds ratio was 2.04, with a mid-p corrected 95 percent confidence interval ranging from 1.10 to 3.82. The hypothesis that the true odds ratio is equal to 1 (i.e., no treatment effect) is rejected ($P = 0.02$, one-tailed exact test); thus, heparin was more antithrombotic than the placebo. In the subgroup analysis with 162 patients mobilized on the fourth day (early), the incidence of thromboembolism was 23 percent in the heparin group and 44 percent in the placebo group, a difference that was even more significant ($P = 0.003$, one-tailed, exact test in a 2 by 2 table), whereas in the 28 patients with delayed mobilization, there was no significant treatment effect ($P = 0.91$, one-tailed, exact test in a 2 by 2 table; Table 3). The location of the thrombi did not differ in the groups. Isolated distal thrombosis was uncommon in both groups (Table 2).

The postoperative blood loss was higher in the heparin group ($P = 0.05$), but there was no difference between the groups concerning the total amount of blood lost (Table 4). The total number of blood transfusions given was higher in the heparin

Table 4. Blood losses and transfusion requirements. Mean (range)

	Heparin (n 105)	Placebo (n 104)
Blood loss (L):		
Operative	0.92 (0.20–2.90)	0.85 (0.20–1.90)
Postoperative[a]	0.59 (0.02–2.20)	0.56 (0.05–2.76)
Total	1.51 (0.50–4.00)	1.41 (0.48–3.51)
Transfusion requirements (units):		
Operative	1.86 (0–6)	1.70 (0–6)
Postoperative[b]	0.87 (0–5)	0.51 (0–3)
Total[b]	2.74 (0–8)	2.22 (0–6)

[a] $P = 0.05$ (Wilcoxon one-tailed test).
[b] $P = 0.02$ (Exact test, one-tailed).

Table 5. Preoperative and postoperative levels of hemoglobin (mmol/L). Mean *SD*

	Heparin (n 103)	Placebo (n 99)
Preoperative	8.5 *0.90*	8.5 *0.99*
Postoperative[a]	6.9 *0.63*	7.1 *0.68*

[a] Average of 7 days. $P = 0.008$ (Student's *t*-test, two-tailed).

group than in the placebo group ($P = 0.019$), but the difference developed mainly during the postoperative period. The decrease in hemoglobin from preoperative to postoperative level in the heparin group significantly exceeded that observed in the placebo group (Table 5).

Two patients died during the study. In the heparin group a man of 79 died on the 11th postoperative day of uncompensated heart failure. At autopsy, small emboli were found in the left lung. Bilateral phlebography 3 days earlier was normal. In the placebo group a woman of 67 died 5 days after the operation. An autopsy was not performed, but the cause of death was probably a rupture of a traumatic aneurysm of the thoracic aorta, resulting from an accident several years before.

Adverse effects, including bleeding complications and wound hematomas, were observed in 13 patients in the heparin group and in 7 patients in the placebo group, a difference that was not significant. Five patients complained of discomfort related to the compression stockings, such as a sensation of heat, pressure, and blister formation, necessitating removal. Sixty-six patients in the heparin group and 20 in the placebo group developed hematomas at the injection sites, but they caused no discomfort.

Discussion

The risk of postoperative thromboembolic complications—DVT and PE—is high in hip surgery. We have previously conducted placebo-controlled studies in both elective and acute hip surgery, and detected incidences of postoperative DVT of 55 and 43 percent, respectively, in patients not receiving prophylaxis (Lassen et al. 1988 and 1989). The majority of thrombi observed in these patients were located in the proximal veins (about 80 percent of all the thrombi in our study were proximal), which more often result in fatal pulmonary embolism than distally located thrombi. Formation of a proximal thrombosis in hip surgery is probably due to a direct influence on the common femoral vein during the surgical procedure, which has recently been visualized in cadaver studies (Planes et al. 1990).

Like the present study, several other controlled studies using LMW heparin, with or without dihydroergotamine, have been able to reduce the incidence of thromboembolic complications after hip surgery (Turpie et al. 1986, Haas et al. 1987, Eriksson et al. 1988, Lassen et al. 1988, Planes et al. 1988). Although direct comparison with other studies using bilateral phlebography is difficult due to differences in LMW heparin and dosage regimen (Turpie et al. 1986, Planes et al. 1988), it may seem that the incidence in our heparin patients was high. Administrative errors can be excluded in our study because every injection of prophylaxis was recorded; and after termination of the study, blood samples from one of the hospitals were analyzed for antifactors IIa and Xa.

The daily dosage of LMW heparin in our patients was based on a dose-finding study performed in abdominal surgery (Hauch et al. 1988), which usually carries a lower risk of postoperative thromboembolic complications than hip surgery. So the suboptimal efficacy in this study may have been due to a too low heparin concentration in our patients. In

current studies with this heparin, the dosage has been increased. We are convinced that the differences in mobilization policy at the wards conducting this study also influenced the outcome, because LMW heparin was not sufficiently effective in patients who had delayed mobilization after operation (Table 3). This observation really seems to be an indirect proof that it is mandatory to avoid delayed mobilization after operations, as has been advocated on empirical basis for decades.

Despite the large number of diagnosed thrombi, none of the patients with DVT developed any clinical symptoms during the present study. In addition to recording the location, we also recorded the size and occlusity of each thrombus. We have published some of these results showing that many thrombi were less than 1 cm in extension and that all of them were nonocclusive at the time of diagnosis (Borris et al. 1989). It emphasizes that in these patients it is not possible to diagnose DVT by means of clinical diagnosis and that diagnostic tests relying on flow alterations due to vein occlusion, such as plethysmography and Doppler ultrasound, will not be useful.

It has been reported that compression stockings have a beneficial prophylactic effect on the number of postoperative thromboembolic complications after hip arthroplasty. In one study, the incidence of phlebographic DVT was reduced from 54 to 20 percent using compression stockings alone (Ishak and Morley 1981). Compared with these results, it seems that stockings alone were not as effective in our patients. The purpose of all the mechanical prophylactic measures is to increase the flow in the veins and thereby reduce the risk of stasis. However, when the proximal veins are almost twisted during the main part of the operation when the hip is dislocated (Planes et al. 1990), it must be difficult to increase the flow to any extent. This may be the reason for the poor outcome in the control group. Hence, from our results, this regimen alone cannot be recommended in hip surgery.

Although the total blood loss was the same in both groups, our finding of lower hemoglobin levels in the heparin group may indicate that some of the blood lost was not recorded because it was located in the deeper layers of the wounds without clinical manifestations. A further confirmation of this hypothesis was our findings that patients treated with heparin had more blood transfusions during the postoperative period. However, the need for blood transfusions, on an average, only amounted to about 150 mL more than was given to patients treated with a placebo.

We gave LMW heparin prophylaxis 2 hours before the operation. Another placebo-controlled study, also in elective hip surgery, reported excellent results by delaying the first prophylactic dose of another LMW heparin until after the operation, up to 24 hours (Turpie et al. 1986). No differences in blood loss or transfusion requirements were detected in that study. However, no other study has been performed to confirm these findings.

In conclusion, thromboprophylaxis with LMW heparin once daily was safe and more effective than placebo in patients undergoing total hip replacement.

Acknowledgements

We wish to thank the chief surgeons of the Departments of Orthopedics at Aalborg Hospital and Århus Municipal Hospital for allowing us to study their patients. We thank Dr. A.-M. Nehen for evaluating the venograms, and Karsten Schmidt (Spadille Aps., Denmark) for statistical advice and discussions of this work.

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