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THE VALUE OF LOW DOSAGE HEPARIN FOR THE PROPHYLAXIS OF THROMBOEMBOLISM IN PATIENTS WITH TRANSCERVICAL AND INTERTROCHANTERIC FEMORAL FRACTURES*

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One hundred and ten female patients, over the age of 60, with intertrochanteric or transcervical femoral fractures were included in a controlled, randomized, clinical trial investigating the value of low dosage heparin in the prophylaxis of deep vein thrombosis. There were 50 completed pairs. Eight (16 per cent) deep vein thromboses occurred in the heparinized group compared with 23 (46 per cent) deep vein thromboses in the control group. The incidence of pulmonary embolism was also reduced. The diagnosis of deep vein thrombosis was made on clinical grounds, supplemented by phlebography and autopsy. There was no difference in the wound haematoma or infection rate. The heparin was commenced on admission to hospital and it is suggested that in this group of patients low dosage heparin prophylaxis should start on admission and not wait until surgery.

Key words: thromboembolism prophylaxis; low dosage heparin; transcervical femoral fractures; intertrochanteric femoral fractures

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Deep vein thrombosis is a frequent complication of fractures of the proximal femur. Using phlebography, Smyrnis et al. (1973) found that deep vein thrombosis had occurred in 60.3 per cent of 58 patients with a fracture of the upper end of the femur. Sevitt & Gallagher (1959) showed that pulmonary embolism was a common cause of death in these patients. Low dosage heparin prophylaxis, which was introduced by Sharnoff & De Blasio (1970), has been found to be a useful method of diminishing the incidence of deep vein thrombosis, following a variety of surgical procedures (Kakkar et al. 1971, Williams 1971, Gordon-Smith et al. 1972, Kakkar et al. 1972). However, little work has been done on its role in patients who have sustained a fracture of the proximal femur. This study was carried out to determine the value of low dosage heparin for the prophylaxis of thromboembolism in patients with trans-

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cervical or intertrochanteric femoral fractures.

PATIENTS AND METHODS

Female patients, over the age of 60 years, who were ambulant before the injury and who had sustained intertrochanteric or transcervical femoral fractures were entered into a controlled, randomized clinical trial. Patients who were under the age of 60, who had a history of deep vein thrombosis, pulmonary embolism, haematemesis, haematuria or other bleeding disorders and patients with malignant disease were excluded from the trial. Male patients were also excluded so that all the patients could be admitted into one ward thus standardizing the nursing care. Patients were stratified according to age and surgical procedure, creating six subgroups (Table 1). The patients were randomly allocated to one of two treatment groups. The first received heparin (BP) 5000 units 12 hourly by deep subcutaneous injection into the abdominal wall, the injections commencing on admission to hospital and continuing until the patient was discharged, transferred or fully mobilized. The second group served as controls. The nursing care was identical in both groups as was the postoperative mobilization. The operative procedure was the same. Drains were not used and, postoperatively, all patients were placed in a cottonwool and crepe bandage hip spica for 48 hours.

Deep vein thrombosis was diagnosed by clinical and venographic techniques. Each patient was examined daily. A positive clinical diagnosis required the presence of peripheral oedema or a 1.5 cm or greater difference in calf circumference in addition to calf or femoral vein tenderness, a positive Homan's sign or pyrexia which otherwise was not explicable. When only peripheral oedema or a difference in calf circumference was found, phlebography was carried out. Some patients who had a definite clinical diagnosis also underwent phlebography, and in these patients the clinical diagnosis was confirmed. Pulmonary embolism was diagnosed on clinical and radiological examination or at autopsy. Lung scans were not used routinely.

Table 1. Stratification of the trial.

	60–74 years	75 years+	Total
Nail fixation only	5	16	21
Nail + plate fixation	8	16	24
Austin-Moore replacement arthroplasty	0	5	5
Total	13	37	50

The number of pairs of patients who were included in each sub-group of the clinical trial.

RESULTS

The results are shown in Table 2. One hundred and ten patients were admitted into the trial and this included 50 randomized, stratified pairs. The results have been determined in these 50 pairs. There were 8 (16 per cent) deep vein thromboses in the heparin-treated group compared with 23 (46 per cent) deep vein thromboses in the control group. This difference is statistically significant ($P < 0.001$). Three patients developed late deep vein thromboses, i.e. thromboses which were found either clinically or at autopsy at least 6 weeks after surgery, where there had been no evidence of deep vein thrombosis in the intervening period and, if the patient was on heparin, after it had been discontinued. There was one late deep vein thrombosis in the heparin group and two in the control group. There was one pulmonary embolus (2 per cent) in the heparin-treated group and two (4 per cent) in the control group. In addition, there were four late pulmonary emboli. These were pulmonary emboli which were found clinically or at autopsy at least 6 weeks after the patient had undergone surgery and where there was no clinical or radiological evidence of the pulmonary embolus in the intervening period. One occurred in a patient who had been on heparin therapy and which had been discontinued when she was mobilized. The other three occurred in control patients. There were 15 deaths in the heparin group and 11 in the control group. All deaths which occurred within 3 months of surgery are included. Ten of the patients in the heparin group died from

Table 2.

	Heparin treated		Control	
No. of paired patients	50		50	
Deep vein thrombosis	8 (16%)*		23 (46%)*	
Pulmonary embolism (Early)	1 (2%)	2 (4%)	2 (4%)	5(10%)
(Late)	1 (2%)		3 (6%)	
Deaths	15 (30%)		11 (22%)	
Wound infection/haematoma	7 (14%)		8 (16%)	
Haematuria	2 (4%)		0	
Cerebrovascular accident	0		1 (2%)	

The results obtained in the 100 paired patients
* This difference is significant ($P < 0.001$).

pneumonia, one from a myocardial infarct, one from pyelonephritis and a cerebral abscess, one following intestinal obstruction and two from pulmonary emboli—at 8 days and 6 weeks. Two patients had a deep vein thrombosis demonstrated at autopsy. Five control patients died from pneumonia, one from a myocardial infarction and five with pulmonary emboli—at 11 days, 4 weeks, 6 weeks, 7 weeks and 8 weeks, respectively. In seven patients deep venous thromboses were present at autopsy.

There were no complications as a result of the heparin therapy. The only patient who had a cerebral vascular bleed was in the control group, but two heparinized patients developed haematuria. The presence of a haematoma and superficial wound infection often occurred simultaneously and these complications, therefore, were considered together. Seven patients in the heparin group developed a haematoma and/or superficial wound infection compared with eight patients in the control group. No patient developed deep infection.

There were 13 pairs between the ages of 60 and 74, and 37 pairs were 75 years or older. The results in these two subgroups are shown in Table 3. The incidence of deep vein thrombosis was higher in the younger age group but again was much less marked in the heparinized patients. In the younger age group, there were three (23.1 per cent) deep vein thromboses in the heparin group compared with eight (61.5 per cent) in the control group. In the older age group there were five (13.5 per cent) deep vein thromboses in the heparin group and 15 (40.5 per cent) in the control group.

The results varied in the different surgical groups and are shown in Table 4. The incidence of deep vein thrombosis was much higher in those patients whose fracture was fixed with a nail and plate

Table 3. The incidence of Deep Vein Thrombosis (D.V.T.) in the two age groups.

	60–74 years		75 years and over	
	No. of patients	No. D.V.T.	No. of patients	No. D.V.T.
Heparinized	13	3 (23.1%)	37	5 (13.5%)
Control	13	8 (61.5%)	37	15 (40.5%)
Total	26	11 (42.1%)	74	20 (27.0%)

Table 4. The incidence of Deep Vein Thrombosis associated with the different surgical procedures.

	Nail fixation		Nail + plate fixation		Replacement arthroplasty	
	No. of patients	No. of D.V.T.	No. of patients	No. of D.V.T.	No. of patients	No. of D.V.T.
Heparinized	21	1 (4.8%)	24	7 (29.2%)	5	0 (0%)
Control	21	5 (23.8%)	24	15 (62.5%)	5	3 (60%)
Total	42	6 (14.3%)	48	22 (45.8%)	10	3 (30%)

than in those whose fractures were fixed with a nail. In 21 pairs the fracture was fixed with a nail. There was one (4.8 per cent) deep vein thrombosis in the heparin group and five (23.8 per cent) deep vein thromboses in the control group. Twenty-four pairs of patients had their fracture fixed with a nail and plate. There were seven (29.2 per cent) deep vein thromboses in the heparin and 15 (62.5 per cent) deep vein thromboses in the control group. Only five pairs of patients had a primary Austin-Moore replacement arthroplasty. The numbers are too small for comparison with the other groups of patients but, nevertheless, there was still a marked difference between the control and heparin groups. There were no deep vein thromboses in the treated group compared with three (60 per cent) in the control group.

DISCUSSION

Patients who sustain an intertrochanteric or transcervical femoral fracture generally tend to be elderly and ill, and the injury is associated with a high mortality and morbidity. The development of a painful deep vein thrombosis or a swollen limb secondary to a deep vein thrombosis interferes with their rehabilitation, whereas an asymptomatic minor thrombosis in the soleal venous plexus does not affect their mobilization. For this reason the diagnosis of deep vein thrombosis was based on clinical findings supplemented by phlebography or autopsy. Similar diagnostic criteria were used by Kline and his colleagues (Kline et al. 1975) in their study.

During the past few years several methods of deep vein thrombosis prophylaxis have been described. Calf compression or stimulation is largely impracticable in patients undergoing hip surgery and was not considered for this study.

Anticoagulation is probably the most established form of prophylaxis. Sevitt & Gallagher (1959) investigated 300 patients, over the age of 55, with a transcervical or intertrochanteric femoral fracture. Half the patients were anticoagulated and half acted as controls. Four (2.7 per cent) clinically detectable deep vein thromboses occurred in the anticoagulated group compared with 43 (29 per cent) in the control group. There were 25 deaths in the treated and 42 in the control group. Autopsy study disclosed deep vein thromboses in three out of 21 (14 per cent) anticoagulated patients compared with 29 thromboses in 35 control patients (83 per cent). Three anticoagulated patients were found to have a pulmonary embolism. In two it was large and thought to have contributed to the cause of death. There were 21 pulmonary emboli including 15 major ones found at autopsy in the control group.

Salzman et al. (1966) also investigated the use of anticoagulants in 166 patients with proximal femoral fractures. They found two (2.4 per cent) deep vein

thromboses in the 83 anticoagulated patients and 22 (26.5 per cent) venous thromboses in their control group. There was one pulmonary embolus (1.2 per cent) in the anticoagulated and eight (9.6 per cent) in the control group. However, they found that anticoagulation was associated with an increase in the wound haematoma rate. There were 29 wound haematomata (34.9 per cent) in the anticoagulated group compared with 20 (24 per cent) in the control group.

In addition to the increased risk of wound haematoma formation, the level of anticoagulation may be difficult to regulate. There is no standard dose; different patients react differently to the same dose and the same patient may react differently on a different occasion. Hypnotics, particularly barbiturates, tend to interfere with their action. In a retrospective study Muckle et al. (1974) found that anticoagulation reached therapeutic levels in only 169 (65 per cent) of 260 patients. The anticoagulation was inadequate in 79 and excessive in 12 patients. When it was inadequate, it did not diminish the incidence of deep vein thrombosis or pulmonary embolism and when excessive was associated with a marked increase in the incidence of wound haematoma formation. Daily estimation of the prothrombin time is essential until control is established and this requires adequate laboratory back-up facilities.

Low dosage heparin prophylaxis, introduced by Sharnoff & De Blasio in 1970, seems to overcome some of the disadvantages associated with other methods. The results obtained in a variety of trials indicate that it is a useful method of diminishing the incidence of deep vein thrombosis (Kakker et al. 1971, Williams 1971 and Gordon Smith et al. 1972). In 1973 Sharnoff stated that he had had only two failures, confirmed at autopsy, compared with more than 1,450 successfully heparinized patients. Interestingly, both failures occurred in elderly patients with a fracture of their proximal femur.

Patients who sustain intertrochanteric and transcervical femoral fractures tend to be immobile from the time of injury whereas patients who undergo major elective surgery are mobile until the time of operation. We decided, therefore, to start our heparin regimen on admission and not to wait until the patient had undergone surgery. This was not associated with any excess bleeding during the operation nor with an increased wound haematoma or infection rate. The results of our study indicate that when heparin is started at this time there is a marked decrease in the incidence of deep vein thrombosis. This is not surprising as one of the main predisposing causes of deep vein thrombosis is immobility.

One of the surprising findings in our study was that the incidence was higher in the 60–74 age group than in the over 75 year age group. Previous work had suggested that the incidence increases with increasing age (Sevitt & Gallagher 1961). Another interesting finding is that the incidence was higher in patients undergoing nail and plate fixation compared with those undergoing nail fixation of their fracture.

In our study sodium heparin (BP) was used, and the results indicate that it is as effective as the more expensive slow release calcium heparin.

Van Vroonhoven (1974), in a controlled clinical trial using I^{125} labelled fibrinogen, found that low dosage subcutaneous heparin was more effective in preventing postoperative deep vein thrombosis than routine oral anticoagulation. There was one (2 per cent) deep vein thrombosis in the 50 patients treated with heparin and nine (18 per cent) in the 50 patients who were anticoagulated.

Gallus et al. (1973) used a modified low dosage heparin regimen consisting of 5,000 units given thrice rather than

twice daily. They investigated 46 patients with fractures of the proximal femur and found 13 per cent deep vein thromboses in the treated group compared with 48 per cent in their control group. In this group of patients the heparin was started within 12 hours of hospitalization. Although clinically significant bleeding was not increased, the amount of blood required for transfusion was moderately increased and the haematocrit was lower, suggesting that the increased dose was associated with increased bleeding. Their incidence of deep vein thrombosis in patients with fractures of their proximal femur were similar to those reported in our study, both in the control and the heparin groups even though they relied on I^{125} labelled fibrinogen uptake for the diagnosis. The similarity in results suggests that the efficacy of the low dosage heparin prophylaxis was due to starting treatment soon after the patient was admitted and was not due to increasing the dose of heparin to 5,000 units thrice daily. Nevertheless, a randomized trial comparing these two low dosage heparin regimens in patients with proximal femoral fractures may be indicated.

The heparin must be continued until the patient is mobile, and this may be partially responsible for the failure reported by Kakkar et al. (1972).

The other major method of deep vein thrombosis prophylaxis is the use of Dextrans, but they may be associated with increased wound haematoma formation and are contraindicated if the blood urea is elevated or renal function is impaired. Korvald et al. (1973) reported that Dextran-70 was relatively ineffective compared with the combination of Dextran-70 and Warfarin in the prophylaxis of deep vein thrombosis in patients with transcervical and intertrochanteric fractures. They also found a different incidence of deep vein thrombosis in the different operative groups which was similar to that found in our study. Wedge et al. (1974) found that Dextran-75 did not significantly alter the thromboembolic complication rate in the patients with hip fractures. These results suggest that Dextran is not as effective as anticoagulation or low dosage heparin in the prevention of deep vein thrombosis.

The mechanism of action of the low dosage heparin is not certain. It is thought that it decreases platelet adhesiveness and inhibits activated factor X. The latter is involved in the process of coagulation. Heparin in the dose used does not affect the thrombin clotting time and does not require laboratory control. The heparin dose can be easily reversed and, therefore, can be used in patients with a past history of haematuria and other bleeding disturbances.

The results of our study indicate that low dosage heparin is a useful method of diminishing the incidence of deep vein thrombosis in patients with transcervical or intertrochanteric fractures. Comparison of our results with other series suggests that, in these patients, it is essential to start the heparin on admission to hospital. When the heparin was commenced at the time of surgery, the incidence of deep vein thrombosis was not reduced. Our findings also indicate that low dosage heparin is at least as good a prophylactic agent as anticoagulants. It has several advantages over other methods in that it is easier to control, does not require routine laboratory studies and is not associated with an increased incidence of wound haematoma. The main disadvantage is that the injection may, on occasions, be uncomfortable.

REFERENCES

Gallus, A. S., Hirsh, J., Tuttle, R. J., Trebilcock, R., O'Brien, S. E., Carroll, J. J., Minden, J. H. & Hudecki, S. M. (1973) Small subcutaneous doses of heparin in prevention of venous thrombosis. *New Engl. J. Med.* **288**, 545–551.

Gordon-Smith, I. C., Grundy, D. J., Le Quesne,

L. P., Newcombe, J. F. & Bramble, F. J. (1972) Controlled trial of two regimens of subcutaneous heparin in prevention of post-operative deep vein thrombosis. *Lancet* **i**, 1133–1135.

Kakkar, V. V., Corrigan, T., Spindler, J., Fossard, D. P., Flute, P. T., Crellin, R. Q., Wessler, S. & Yin, E. T. (1972) Efficacy of low doses of heparin in prevention of deep vein thrombosis after major surgery. *Lancet* **ii**, 101–106.

Kakkar, V. V., Field, E. S., Nicolaides, A. N., Flute, P. T., Wessler, S. & Yin, E. T. (1971) Low doses of heparin in prevention of deep vein thrombosis. *Lancet* **ii**, 669–671.

Kline, A., Hughes, L. E., Campbell, H., Williams, A., Zlosnick, J. & Leach, K. G. (1975) Dextran 70 in prophylaxis of thromboembolic disease after surgery: a clinically orientated randomized double-blind trial. *Brit. med. J.* **2**, 109–112.

Korvald, E., Støren, E. J. & Ongre, A. (1973) Simultaneous use of warfarin-sodium and dextran 70 to prevent post-operative venous thrombosis in patients with hip fractures. A controlled trial. *J. Oslo Cy Hosp.* **23**, 25–34.

Muckle, D. S., Forney, H. J. & Bentley, G. (1974) The value of prophylactic anticoagulant therapy with warfarin after hip surgery. *Acta orthop. scand.* **45**, 412–420.

Salzman, E. W., Harris, W. H. & De Sanctis, R. W. (1966) Anticoagulation for prevention of thromboembolism following fractures of the hip. *New Engl. J. Med.* **275**, 122–130.

Sevitt, S. & Gallagher, N. G. (1959) Prevention of venous thrombosis and pulmonary embolism in injured patients. *Lancet* **ii**, 981–989.

Sevitt, S. & Gallagher, N. G. (1961) Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. *Brit. J. Surg.* **48**, 475–489.

Sharnoff, J. G. (1973) Prevention of thromboembolism. *Bull. N.Y. Acad. Med.* **49**, 655–660.

Sharnoff, J. G. & DeD Blasio, G. (1970) Prevention of fatal postoperative thromboembolism by heparin prophylaxis. *Lancet* **ii**, 1006–1007.

Smyrnis, S. A., Kolios, A. S. & Agnantis, J. K. (1973) Deep vein thrombosis in patients with fractures of the upper part of the femur. A phlebographic study. *Brit. J. Surg.* **60**, 447–450.

van Vroonhoven, T. J. M. V., van Zijl, J. & Muller, H. (1974) Low-dose subcutaneous heparin versus oral anticoagulants in the prevention of postoperative deep venous thrombosis. A controlled clinical trial. *Lancet* **i**, 375–377.

Wedge, J. H., Kirkaldy-Willis, W. H. & Hayton, R. C. (1974) Dextran 75 in the prophylaxis of deep venous thrombosis and pulmonary embolism. *Canad. J. Surg.* **17**, 45–48.

Williams, H. T. (1971) Prevention of post-operative deep vein thrombosis with peri-operative subcutaneous heparin. *Lancet* **ii**, 950–952.

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