

A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement

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Summary

In a randomized, controlled clinical study, dextran-70, warfarin, or low-dose heparin were administered to patients undergoing total hip replacement on one surgical unit in an attempt to prevent deep venous thrombosis and pulmonary embolism. Calf vein thrombosis was detected by the ^{125}I -fibrinogen uptake test. None of the methods prevented calf vein thrombosis (dextran-70, 51%; warfarin, 58.6%; heparin, 52.6%). Pulmonary embolism was completely prevented in patients treated with warfarin but occurred in 4% of patients treated with dextran-70 and 15.5% of those treated with low-dose heparin. The incidence of complications of therapy was small and comparable in each group. It is suggested that calf vein thrombosis is a frequent and in itself a non-serious complication of total hip replacement surgery and that emphasis might be placed more usefully on prevention of pulmonary embolism.

Introduction

Elective orthopaedic procedures such as total hip replacement performed on patients of advanced age pose a particular problem in management. There is a greater incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) in this than in any other group of surgical patients, with a DVT rate of 50-54% and pulmonary embolism rate of 4-12.5% (Evarts and Feil, 1971; Hampson *et al.*, 1974; Morris, Henry and Preston, 1974). Many attempts have been made to avert the important complication of pulmonary embolism by preventing deep venous thrombosis in the calf, on the assumption that all

thrombi originate in the calf veins and extend proximally before embolism occurs. Strong claims have been made for the efficacy of low-dose heparin (Kakkar *et al.*, 1972; Morris *et al.*, 1974) in preventing calf thrombi, but other reports have not been confirmatory (Hampson *et al.*, 1974; Harris *et al.*, 1974). Dextran-40 (Evarts and Feil, 1971) and dextran-70 (Bonnar and Walsh, 1972) have also reduced the incidence of calf thrombosis dramatically but total prevention has been achieved rarely. Moreover, various authors have reported 'silent' pelvic vein thrombosis with subsequent pulmonary embolism in the absence of calf vein thrombosis in up to 50% of cases (Sevitt and Gallagher, 1959; Mavor *et al.*, 1972; Harris *et al.*, 1974). The oral anticoagulants phenindione (Sevitt and Gallagher, 1959) and warfarin (Harris, Salzman and de Sanctis, 1967; Harris *et al.*, 1972; Muckle, Forney and Bentley, 1974) have been reported as preventing pulmonary embolism completely although bleeding complications have occurred in a small percentage of cases following hip surgery and dosage control has sometimes proved difficult (Muckle *et al.*, 1974).

In view of the uncertainty of the efficacy of current methods of preventing deep venous thrombosis and pulmonary embolism a prospective, randomized, controlled clinical trial was set up in one surgical unit, in which techniques of pre-, per- and post-operative management were as standard as possible. Previously, warfarin therapy had completely prevented pulmonary embolism following total hip replacement in this unit (Muckle *et al.*, 1974). Accordingly, a comparison of the effect of low dose

heparin administered twice daily, dextran-70, and warfarin commencing 36 hr after operation, on the whole pattern of deep venous thrombosis and pulmonary embolism was made. Dextran-70 was chosen in preference to dextran-40 because of its longer half-life in the circulation (40% excretion in 24 hr) and presumed more uniform anticoagulant effect, and its reported efficacy in prophylaxis of deep venous thrombosis (Bonnar and Walsh, 1972). A control group was not considered justifiable in view of previous experience on this unit with warfarin and a review of the literature.

Patients and methods

Between February 1973 and October 1975 all patients admitted to the Nuffield Orthopaedic Centre for total hip replacement, under the care of one surgical team, were considered for inclusion in the trial. Those with the following conditions were excluded:

(1) Past history of malignancy, thrombo-embolism or peptic ulceration.

(2) Steroid or salicylate therapy. This excluded patients with rheumatoid arthritis.

All suitable patients were randomly allocated to a treatment group. On the day before surgery the patient was given 120 mg potassium iodide orally; this dose was continued daily until the patient was discharged from hospital. All patients had a Charnley-type of total hip prosthesis implanted. Immediately after operation, 100 μ Ci of 125 I-labelled fibrinogen (supplied by the Radiochemical Centre, Amersham) were administered intravenously. At the end of the operation the limb was placed on a Hodgen's splint and active contraction of all leg muscles was encouraged on recovery of consciousness. Thereafter, the patients spent 1 hr each morning and afternoon performing active exercises under the supervision of a physiotherapist, with as much movement as possible at all times. After 10 days the splints were removed and sling exercises commenced in bed. Walking with crutches began 10–14 days after operation.

Independent scanning and clinical examination of the legs were performed daily until the patients were mobilizing freely with crutches, between 11 and 14 days postoperatively.

Details of treatment

(1) Dextran-70 was administered as 1000 ml starting with induction of anaesthesia, 1000 ml daily for 3 days and then 500 ml on alternate days for 10 days. Blood urea and electrolyte levels were monitored daily during dextran therapy as a guide to renal function.

(2) Warfarin was begun 36 hr after surgery; 15 mg loading dose was followed by none on the next

day and 5 mg on the day after that. Thereafter the dosage was adjusted to maintain a prothrombin time of 10–20% and continued for 3 weeks.

(3) Heparin, 5000 units, was given subcutaneously into the abdominal wall at 12 hr intervals commencing on the evening before surgery, for 3 weeks.

The scanning technique was that described by Atkins and Hawkins (1965). Measurement was performed with a Ratemeter, Type R.M.5 (Nuclear Enterprises U.K.) at points 10 cm apart on the medial aspect of the leg beginning at the medial malleolus. A change of 20% in the count between adjacent points, persisting for 48 hr, was considered diagnostic of deep venous thrombosis. Venograms were performed on patients with calf thrombosis who had clinical evidence of proximal propagation such as oedema or tenderness over the thigh vessels. Pulmonary embolism was confirmed by lung field scanning.

Results

Of the 128 patients included in the trial, seventy-eight were female and fifty were male. Ages ranged from 39 to 85 years, with a mean of 65.5 years (Fig. 1).

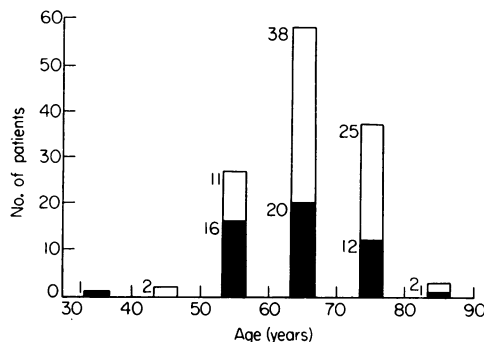


Fig. 1. Histogram to show age and sex distribution of patients. □, female; ■, male.

Deep vein thrombosis

Deep venous thrombosis developed in seventy patients (54.7%). There was no significant difference in the incidence of deep venous thrombosis in the distal veins in those patients receiving dextran-70 compared with twice-daily subcutaneous heparin ($\chi^2=3.02$; d.f. = 1; $0.10 > P > 0.05$), warfarin compared with heparin ($\chi^2=0.21$; d.f. = 1; $1.0 > P > 0.10$), or dextran-70 compared with warfarin ($\chi^2=0.64$; d.f. = 1; $1.0 > P > 0.10$).

Pulmonary embolism

There were five episodes of pulmonary embolism overall. Three of these were in the first nineteen

patients (15.8%) who received subcutaneous heparin and one was fatal. Post-mortem confirmed pulmonary embolism which was from thrombosis in the right femoral vein although scanning and clinical examination had shown no evidence of deep venous thrombosis, suggesting a pre-operative thrombus. At this point the heparin trial was discontinued. The other two emboli were in patients receiving dextran (4%) and one of these was fatal. Neither patient had a calf thrombosis up to 14 days after operation.

Results in the three treatment groups

(1) *Dextran* (Table 1). Of fifty-one patients (eighteen male, thirty-three female) who received dextran-70, twenty-six had calf DVT (51%).

TABLE 1. Dextran—incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Sex	Male		Female		Total
	<70	>70	<70	>70	
Age (years)	<70	>70	<70	>70	
Patients	14	4	25	8	51
DVT	4	2	15	5	26 (51%)
No DVT	10	2	10	3	25
PE	0	1	0	1	2 (4%)
No PE	14	3	25	7	49

There was no significant difference at the 5% level between patients of 70 years and younger compared with those 71 years or older, or between the sexes at any age. Pulmonary embolism occurred in two patients (4%) and was fatal in one of these. Whilst in hospital, there had been no evidence of DVT in either patient and the embolic episodes developed 31 and 38 days after operation. Thus the emboli almost certainly arose from 'silent' thrombi above the calf vessels.

(2) *Warfarin* (Table 2). Of fifty-eight patients who received warfarin (twenty-two male, thirty-six female), thirty-four (58.6%) had DVT.

TABLE 2. Warfarin—incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Sex	Male		Female		Total
	<70	>70	<70	>70	
Age (years)	<70	>70	<70	>70	
Patients	16	6	24	12	58
DVT	6	5	14	9	34 (58%)
No DVT	10	1	10	3	24
PE	0	0	0	0	0
No PE	16	6	24	12	58

There was a significantly decreased incidence of DVT in those patients receiving warfarin aged 70 years or less compared with the older group ($P=0.047$) but no significant difference occurred between the sexes in either group or in total. No pulmonary embolism was recorded in this group.

(3) *Heparin* (Table 3). Only nineteen patients received heparin (eight male, eleven female) and ten of these had DVT (52.6%) before the group was discontinued.

TABLE 3. Heparin—incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Sex	Male		Female		Total
	<70	>70	<70	>70	
Age (years)	<70	>70	<70	>70	
Patients	6	2	6	5	19
DVT	1	2	3	4	10 (52%)
No DVT	5	0	3	1	9
PE	1	0	1	1	3 (15.8%)
No PE	5	2	5	4	16

Although the numbers were small there was a significant lessening of DVT in the younger age group ($P=0.04$) but no difference could be related to sex.

Three patients on this regime developed pulmonary embolism within 12 days of operation; one of these was fatal. The fatality occurred 8 days postoperatively with no clinical evidence of DVT and a negative scan, suggesting a pre-operative thrombosis. Thrombosis and embolism were diagnosed at post-mortem. The other two patients with pulmonary emboli had a positive calf vein scan. The emboli occurred at 1 and 12 days and were confirmed by pulmonary scanning.

Complications of treatment

Wound haematoma. Wound haematoma occurred in thirty patients (23%). Fourteen had received warfarin; thirteen, dextran; three, heparin; only one haematoma was large enough to require surgical evacuation and all healed satisfactorily. No bleeding occurred from other sites.

Wound infection. There were no deep wound infections.

Complications of dextran-70 therapy. Four patients developed complications with dextran-70 which necessitated cessation of the infusions. One developed an allergic reaction to dextran, one persistent bleeding at the drip site, one a raised blood urea and one congestive cardiac failure. Two others had their infusions stopped in error by the nursing staff. The dextran-70 infusions were resented by some of the patients since they interfered with freedom of movement and they required close supervision by the nursing and medical staff.

Discussion

Deep vein thrombosis

The overall incidence of DVT in the distal veins in this series (54.7%) is considerably higher than the 32% untreated patients, and the 36% treated with

warfarin, detected by Pinto (1970) using the radioisotope method, although his patients included some with hip fractures who have a lower incidence. The incidence approximates closely to the 53.6% of Evarts and Feil (1971), the 54% of Hampson *et al.* (1974) and 50% of Morris *et al.* (1974) occurring in untreated patients. The present authors conclude that either the incidence of deep venous thrombosis in untreated patients in this high-risk group is higher than 55% or the incidence of DVT in untreated patients is of the order of 55% and the methods used in this trial had no prophylactic effect. The reasons for this may be: (a) heparin was given only twice daily and this probably is insufficient. Individual response to heparin is very variable (Brozovic *et al.*, 1974); (b) warfarin was not begun until 36 hr after operation and the majority of calf thrombi have formed by this time (Hampson *et al.*, 1974); (c) dextran-70 was administered according to a regime which is not prophylactic in terms of dose or timing.

A review of the literature shows that complete prevention of calf thrombi has never been achieved in this high-risk group of patients by any agent. Moreover, 'silent' thrombosis may occur in the proximal deep veins in the absence of thrombi in the calf veins. Therefore, the use of the absence of calf vein thrombosis as a criterion of the success of a regime to prevent thromboembolism is invalid in this group of patients.

Pulmonary embolism

The results show that pulmonary embolism was not prevented by heparin or dextran-70 where the incidence was 15.8% and 4% respectively. In the dextran group the onset of embolism was postponed until 31 and 38 days after operation, but embolism was within 12 days of surgery in the three cases receiving heparin. In the fifty-eight patients receiving warfarin no pulmonary embolism occurred. This accords with the findings of Harris *et al.* (1967, 1974) that no emboli occurred in patients receiving warfarin following hip replacement procedures.

Complications of therapy were no greater with warfarin than with heparin and dextran-70. The incidence of wound haematomata was not significantly different in the three groups. Haemorrhage from other sites did not occur in any group, and the wound sepsis rate was zero. Warfarin was subjectively reported by the patients, and by the medical and nursing staff, to be the easiest therapy to administer, although it involves the most laboratory effort, cost and time, and dextran-70 the most difficult.

On the basis of this investigation the authors

recommend the use of warfarin as a safe method for the prophylaxis of pulmonary embolism, following total hip replacement, in preference to dextran-70 or twice-daily subcutaneous heparin. Its effects might be increased by commencing administration before operation as suggested by Harris *et al.* (1974).

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