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PROPHYLAXIS OF DEEP VEIN THROMBOSIS IN PATIENTS WITH FRACTURE OF THE FEMORAL NECK

A Prospective Comparison between Dextran and a Sulphated Polysaccharide

H. O. FREDIN, S. A. NILLIUS & D. BERGQVIST[1]

Departments of Orthopaedic Surgery and General Surgery[1], Malmö General Hospital (University of Lund), Malmö, Sweden

A prospective and randomized study of 100 patients with fracture of the femoral neck was carried out. The aim was to compare the thromboembolic prophylactic effect of dextran 70 and a sulphated polysaccharide, PZ 68. Deep vein thrombosis was diagnosed using the ^{125}I-fibrinogen test and phlebography, and pulmonary embolism with a perfusion and ventilation scan. The number of thromboses and emboli did not differ significantly between the two groups. However, there was a general tendency for predominance of thrombosis on the operated side. Six patients were excluded in the PZ 68 group because of major haemorrhage.

Key words: dextran; hip fractures; polysaccharides; postoperative complications; thromboembolism

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Ever since Ahlberg et al. (1968) demonstrated the thromboprophylactic effect of dextran in patients with hip fracture, this prophylactic method has been used in the Department of Orthopaedic Surgery, Malmö General Hospital.

The prophylactic effect of oral anticoagulants has also been proven (Sevitt & Gallagher 1959). Their effect is equal to that of dextran 70 (Bergquist et al. 1972). However, there is a real risk of severe haemorrhage when peroral anticoagulative prevention is used. Moreover, peroral prevention is cumbersome because of the continuous laboratory checks which are required. Subcutaneous, low-dose heparin, highly effective in general surgery (Kakkar 1978), has a considerably reduced effect in patients with hip fractures (Bergqvist et al. 1979). Kakkar et al. (1972) also found indications that patients with hip fractures do not respond to low doses of heparin.

A new generation of agents preventing thromboembolism are the heparinoids or glucosaminoglycans, one of which is sodium pentosan polysulphate (PZ 68). This semi-synthetic substance from the vegetable kingdom is a sulphated xylan. The molecular weight is low (approximately 4,000) and it has a narrow distribution. Preliminary results have demonstrated an increased inhibitor activity of factor Xa (Yin et al. 1978). It is thereby theoretically possible that the increase of factor Xa, which develops after trauma, could be counteracted.

The purpose of this prospective study was to compare sodium pentosan polysulphate with dextran 70 in thromboembolic prevention after hip fracture surgery.

PATIENTS AND METHODS

The study has been approved by the Ethics Committee, University of Lund, and the substance (PZ 68) passed by the Pharmaceutical Department of the National Social Welfare Board.

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Table 1. Reasons for exclusion from the study

	PZ 68	Dextran
Technical reasons	12	4
Complicating diseases		
Acute heart attack	1	
Senility	1	2
Severe, rheumatoid arthritis	1	
Plaster of Paris on lower limb		1
Cardiac insufficiency		1
Primary total hip replacement		1
Sitting position due to cardiac insufficiency	1	
Complications of treatment		
Haematuria	2	
Haematemesis	1	
Major wound haematoma	3	
Total	22	9

One hundred consecutive patients with a fracture of the femoral neck were allocated at random to two groups using sealed envelopes. Allocation was made when the patients entered the Emergency Unit at the Department of Orthopaedic Surgery.

Immediately after diagnosis, reposition of the fracture was carried out by extension from a pin inserted through the tibial tubercle.

The operation was performed with closed reduction of the fracture on an extension table and subsequent percutaneous nailing of the fracture using the Rydell nail. Epidural anaesthesia was used. Full weight-bearing was allowed postoperatively as soon as possible, i.e. on the 1st to the 3rd day.

Thirty-one patients were excluded from the study, mainly for technical reasons. However, there were also complicating diseases and major haemorrhage resulting in the termination of the prophylactic agent (Table 1). The clinical material left for analysis is presented in Table 2.

PZ 68 (prepared by Benechemic GmbH, Munich, Germany, under the name of SP 54 and provided by Pharmacia AB, Uppsala, Sweden) was administered subcutaneously in a dose of 75 mg every 12 hours for 8 days. The first injection was given in the Emergency Unit. The upper arm was chosen as the site of injection. Every injection was recorded by the donor on a check-list, which followed the patient. Dextran 70 (Macrodex® 6 per cent in saline, Pharmacia AB, Uppsala, Sweden) was given in a dose of 500 ml, corresponding to 30 g, peroperatively and on the second postoperative day.

The ^{125}I-fibrogen uptake test was used as an objective method for detecting deep vein thrombosis. Immediately before the operation 100 microCurie of ^{125}I-fibrinogen was given intravenously, after having blocked the thyroid gland with peroral iodine (300 mg KI, 1 × 1 × XIV). Daily measurements were made postoperatively for 7–8 days from the sole of the foot up to the distal part of the thigh. The uptake was related to heart activity. An increase of 20 per cent or more between two adjacent points, in two or more consecutive measurements, was considered diagnostic for deep vein thrombosis. If the ^{125}I-fibrinogen uptake was positive, an ascending phlebography and a perfusion-ventilation lung scan were performed. Macroaggregated albumin labelled with ^{99m}Tc was used intravenously in the perfusion lung scan and ^{99m}Tc-aerosol in a ventilation scan when it was found necessary to confirm the diagnosis.

Pulmonary embolism was considered present if a perfusion defect of at least segmental size was found without a corresponding ventilatory defect.

RESULTS

A diagnostic flow diagram can be followed in Figure 1. The frequency of a positive ^{125}I-fibrinogen uptake in the PZ 68 group was 26 per cent and in the dextran 70 group 32 per cent. The difference is not significant.

The phlebography following a positive uptake showed deep venous thrombosis in 6 cases of the PZ 68 group (21 per cent) and in 8 out of 12 in

Table 2. Clinical parameters of the two prophylactic groups

	Sex		Age	Fractured hip		Interval of time between trauma and operation (days)
	Male	Female	years	Right	Left	
PZ 68	5	22	73.7±10.8	13	14	1.5±0.9
Dextran 70	12	29	76.7±11.0	16	25	1.4±0.8
Total	17	51	75.5±10.9	29	39	1.5±0.9

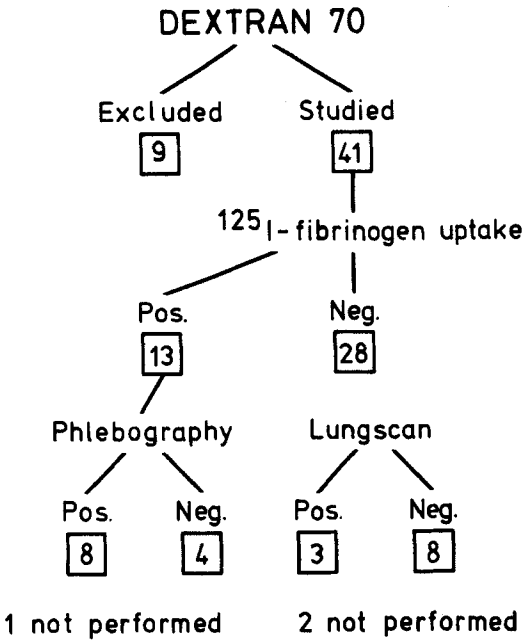

Figure 1a. Patients treated with Dextran 70.

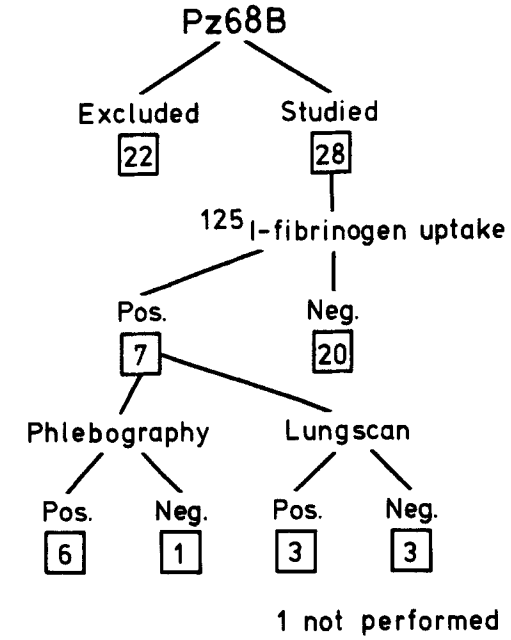

Figure 1b. Patients treated with PZ 68.

the dextran 70 group (20 per cent). Table 3 shows the rate of positive results of the operated as well as non-operated side.

Lung scanning was positive for pulmonary embolism in 3 cases out of 6 in the PZ 68 group compared with 2 out of 9 in the dextran 70 group.

The peroperative blood loss and the transfusion requirement can be studied in Table 4.

Looking at the complications (Table 5), there were 4 cases of wound haematoma in the PZ 68 group compared with 2 cases in the dextran 70 group. Eleven PZ 68 patients had a haematoma at the site of injection. Six patients were excluded in the PZ 68 group because of major haemorrhages (Table 1). The treatment was conservative in every case except in one wound haematoma,

Table 3. Number of deep vein thromboses

	Operated side/Nonoperated side	
	Positive ^{125}I-fibrinogen	Positive phlebography
PZ 68	5/2	5/1
Dextran 70	10/3	6/2
Total	15/5	11/3

Table 4. Peroperative blood loss and transfusion requirement

	n	Peroperative bleeding (ml)	Total units of blood transfused		
			Perop.	Postop. day 1–5	6–14
PZ 68	27	15±36	0	2	4
Dextran 70	41	55±96	0	0	6
	$P<0.05$				

Table 5. Complications

	Injection haematoma	Minor wound haematoma	Major haemorrhage
PZ 68 B	11	4	6
Dextran	1	2	0

Table 6. Mortality

	Pulmonary embolism	Other causes	Total (within 30 days, %)
PZ 68	1	1	7.4
Dextran 70	0	4	9.8

which required a surgical intervention. One patient died from a bleeding duodenal ulcer.

No anaphylactoid reaction or cardiac insufficiency was recorded after administration of dextran 70. As can be seen in Table 6, there was one case of fatal pulmonary embolism. This patient had a fall 2 weeks earlier resulting in an undislocated cervical fracture, which later brought her to hospital because of persistent pain. Death occurred on the 3rd postoperative day. Myocardial infarction and bronchopneumonia were the other causes of death.

DISCUSSION

Prophylaxis of thromboembolism is nowadays a well documented routine in high-risk patients. Therefore, we did not find it satisfactory from an ethical point of view to perform the study with an untreated control group. It also seemed reasonable to use an established method for comparison, and therefore dextran 70 was chosen.

As the sulphated polysaccharide, PZ 68, belongs to a new generation of thromboprophylactic substances, the glucosaminoglycans, we found good reasons for an evaluation. Its mechanism of action resembles that of heparin (Bergqvist & Nilsson 1981), although its action as an inhibitor of factor Xa is a little more specific (Ryde et al. 1980).

Bergqvist et al. (1980) found that the thromboprophylactic effect of PZ 68 and low dose heparin with dihydroergotamine was equal in elective surgery, and that PZ 68 and dextran 70 have an equal effect in hip fracture surgery. They administered PZ 68 in a dose of 100 mg twice daily. With this dose an increased transfusion requirement arose, especially after elective surgery. We, therefore, considered it important to find out if a lower dose, 75 mg, would reduce the haemorrhage problem without diminishing the prophylactic effect.

From our present study it can be concluded that PZ 68 and dextran 70 do not differ in prophylactic effect. Neither was there any difference using the ^{125}I-fibrinogen test or phlebography as the diagnostic method. The somewhat higher frequency of thrombosis discovered with the fibrinogen test can be considered as an effect of a higher sensitivity in detecting small thrombi. The increased frequency of deep venous thrombosis in the operated leg might be explained by inadequate muscular function during the postoperative period.

At the same time as our study a randomized, prospective trial was performed with dextran 70 and PZ 68 in a dose of 75 mg in elective abdominal surgery. The reduction of postoperative deep vein thrombosis in the PZ 68 group was obvious and the difference significant (Bergqvist & Ljungnér 1981). Thus, it seems as if the effect of PZ 68 is better in elective abdominal surgery than in hip fracture surgery. The possible reason for this fact might be that the clotting mechanism was already activated by the trauma when the PZ 68 prophylaxis was started in the fractured patient.

There were 11 haematomas at the site of injection in the PZ 68 group, which was an obvious inconvenience to the patient. It is possible that subcutaneous administration in the abdominal wall can diminish the frequency of injection haematoma. Six patients were excluded in the PZ 68 group because of haemorrhage, although it cannot be proven that PZ 68 was responsible. However, the mere suspicion of a connection means that substances influencing haemostasis must be terminated in cases with major haemorrhagic complications.

The peroperative blood loss was low. The significant difference between the groups is without clinical importance.

One drawback that PZ 68 has in common with low dose heparin is the need for frequent administration. In this study PZ 68 was given on 16 occasions compared with the two infusions of dextran 70. In a recent study comparing low dose heparin and dextran it has been shown that a

complete prophylaxis with low dose heparin is hard to obtain owing to the significant number of missed injections (Gruber et al. 1980).

PZ 68 and dextran 70 are equally effective in thromboembolic prophylaxis after hip fracture surgery, but the frequency of administration differs between the two agents. It cannot be excluded that PZ 68 provides more haemorrhage problems. Therefore dextran 70 is still to be recommended for thromboembolic prevention in patients with fractures of the femoral neck.

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Correspondence to: Hans Fredin, M.D., Department of Orthopaedic Surgery, Malmö General Hospital, S-214 01 Malmö, Sweden.