Dextran 70 in Prophylaxis of Postoperative Venous Thrombosis

A Controlled Trial

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Summary: A controlled prospective trial was carried out in a group of 80 women undergoing gynaecological surgery and thought to be at risk of developing postoperative venous thrombosis. The patients, who had been randomly allocated to prophylaxis with either dextran 70 or warfarin, were well matched in age, weight and other predisposing factors.

In the warfarin group, 12 out of 40 patients developed deep vein thrombosis, six of these episodes being classified as major and six as minor. In the dextran 70 group, 4 out of 40 patients developed deep vein thrombosis, all of them minor. The protective effect of dextran 70 is significantly better than that of warfarin ($P < 0.01$) as used in the present study.

Introduction

Necropsy studies have shown that the incidence of venous thrombosis is larger than that suspected from the frequency with which the condition is diagnosed clinically (Gibbs, 1957; Sevitt and Gallagher, 1959). In the past two years the use of ^{125}I -fibrinogen scanning has shown the true incidence of venous thrombosis in groups of patients after operation (Kakkar and Flanc, 1968; Negus *et al.*, 1968). In a study of 111 patients considered to be at high risk of venous thrombosis after operation we have found that nearly half develop the condition and that two-thirds of these episodes are never suspected despite careful clinical appraisal (Lambie *et al.*, 1970). It may therefore be strongly argued that the prevention of pulmonary embolism should depend on the widespread adoption of effective prophylactic measures against venous thrombosis, especially in high-risk patients. The need for prophylaxis in elderly patients with fractures of the femoral neck has long been emphasized, in particular by the work of Sevitt and Gallagher (1959), and specific prophylactic measures have been taken in some departments of gynaecology (Bottomley *et al.*, 1964; Turnbull, 1964). Outside cardiovascular surgery, however, the need for vigorous efforts to prevent postoperative thromboembolic complications in orthopaedic, gynaecological, and general surgical patients is, if not unrecognized, at least largely ignored in this country. Furthermore, the efficacy of various prophylactic measures depends almost exclusively (the studies of Sevitt and Gallagher (1959) excepted) on evaluations based on clinical diagnosis, now known to be highly inaccurate.

The prophylaxis of venous thrombosis is now being looked at afresh, and the use of ^{125}I -fibrinogen as a diagnostic technique has already shown, for example, that the time-honoured dependence on leg exercises and elastic stockings is almost worthless (Flanc *et al.*, 1969). Current interest in the prevention of intravascular thrombosis centres on drugs which affect platelet behaviour and could be expected, therefore, to suppress the thrombotic process at its inception. One such substance is dextran; infusion of dextran 70 (Macrodex) depresses platelet adhesiveness both in normal men (Bennett *et al.*, 1966; Bygdeman and Eliasson, 1967) and in postoperative patients with enhanced platelet adhesiveness (Dhall *et al.*, 1968). Dextran 70 has also a profound suppressive effect on platelet activity at sites of endothelial damage (Arfors *et al.*,

1968), and the antithrombotic properties of dextran have been demonstrated in several experimental studies (Borgström *et al.*, 1959; Bryant *et al.*, 1962; Moncrief *et al.*, 1963; Just-Viera and Yeager, 1964; Winfrey and Foster, 1964).

Controlled clinical trials, in which the diagnosis was based on phlebography carried out some weeks later, have shown that dextran 70 affords significant protection against venous thrombosis in patients with fractures of the femoral neck (Ahlberg *et al.*, 1968; Johnsson *et al.*, 1968). Anticoagulants, however, are widely accepted as effective in the prophylaxis of venous thrombosis by those prepared to face the difficulties in controlling dosage. In the present trial we have compared the efficacy of dextran 70 with that of oral warfarin.

Methods

Eighty patients were studied. All underwent major gynaecological surgery and were considered to be at high risk of developing venous thrombosis. The patients fell into one or other of the following groups: (1) over 45 years and obese—that is, with a weight-to-height ratio expressed in pounds and inches of greater than 2:1; and (2) patients not included in the above group but with a previous history of venous thromboembolism or with gross varicose veins.

Selection of patients was limited to those undergoing either hysterectomy or pelvic floor repair and, after subdivision into these two groups, allocation to one or other prophylactic regimen was effected by a series of random numbers. Accordingly, each treatment group comprised 20 patients undergoing pelvic floor repair and 20 undergoing hysterectomy. In retrospect, the groups were well matched in terms of factors predisposing to venous thrombosis (Table I).

TABLE I.—Analysis of Patients within Each Treatment Group

	Warfarin	Dextran 70
Pelvic floor repair	20	20
Hysterectomy	20	20
Age (mean)	57.9 years	55.9 years
Weight (mean)	68.5 kg.	69.0 kg.
Height (mean)	158.5 cm.	158.1 cm.
Previous thromboembolism	11 (5)	17 (3)
Malignant disease	5 (4)	4 (1)
Varicose veins	12 (5)	12 (2)
Oral contraceptives	5 (0)	5 (1)

Figures in parentheses are the number of patients who developed venous thrombosis.

Warfarin was used according to a regimen in routine use in gynaecological patients in Aberdeen during the past 10 years and believed to be effective, at least in the prevention of pulmonary embolism (Turnbull, 1964). Warfarin sodium was given in a dose of 30 mg. 36 hours after the operation, and subsequent doses were adjusted to maintain the Quick one-stage prothrombin time between 2 and 2.5 times the control value. Dextran 70 in isotonic saline was given intravenously in a dose of 7 ml./kg. body weight during the operation. This was then followed by an infusion of 3.5 ml./kg. daily on each of the first three postoperative days. In patients who were not receiving intravenous fluids for other reasons the postoperative infusions were administered during one to two hours through a 21G. needle, which was thereafter removed. All the patients in the trial were subject to the normal ward routine, which included early visits by the physiotherapist to encourage leg movement and breathing exercises. Each patient received potassium iodide preoperatively and during the first two weeks after operation.

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Immediately after the operation 50 μ Ci of 125 I-fibrinogen was given intravenously. The fibrinogen was prepared as previously described (Lambie *et al.*, 1970) and the legs were scanned according to the method of Negus *et al.* (1968). Scanning was begun on the first postoperative day and was repeated daily for 8 to 10 days.

The criteria for the diagnosis of venous thrombosis were those described by Negus *et al.* (1968). Deep vein thrombosis when diagnosed was arbitrarily classified as either major or minor. The thrombotic process was classified as major if one or more of the following criteria were satisfied: (1) veins above the knee involved; (2) thrombosis below the knee extending over three or more scanning areas—that is, at least 10 cm. long; (3) both legs affected; and (4) associated with pulmonary embolism. Minor thrombotic episodes were those which were detected only in the calf and did not extend beyond one or two of the standard scanning areas.

Results

The results are shown in Table II. Twelve patients who were given warfarin developed deep vein thrombosis. Six

TABLE II

	No. of patients	Major Thrombosis	Minor Thrombosis
Warfarin ..	40	6	6
Dextran 70 ..	40	Nil	4

episodes were classified as major: two patients had bilateral thrombosis below the knee and one of these suffered a pulmonary embolism, three had thigh vein thrombosis, and one had extensive below-knee thrombosis. The other six patients in the warfarin group had minor calf vein thrombi. In the dextran 70 group four patients developed deep vein thrombosis, consisting in each case of a single minor thrombus confined to the calf veins.

To take account of the difference between major and minor episodes the results were analysed with Yeats's (1948) form of the χ^2 which tests for trend. It was found that the validity of this test is not affected by the smallness of some of the expected values, provided, as in this case, the total in each treatment group is reasonably large. This test shows that dextran 70 prophylaxis is significantly better than warfarin ($P < 0.01$).

Discussion

It has been shown that dextran 70 given during operation and for three days afterwards protects high-risk patients against thigh and leg venous thrombosis and is better than warfarin begun 36 hours after operation. It should be noted, however, that in the 16 patients who developed thigh and leg venous thrombosis 10 of the episodes were apparent on the first postoperative day (7 out of 12 in the warfarin group) and quite probably occurred during the operation. Clearly, if anticoagulation is of prophylactic value it must be effectively established at the time of operation and therefore begun at least 36 hours before. This suggestion is not new (Sevitt and Gallagher, 1959), but many clinicians are reluctant to adopt it for fear of bleeding. Another drawback to the use of oral anticoagulants is difficulty in controlling dosage.

The anticoagulant regimen evaluated in this trial had been in routine use for several years and the ward staff were thoroughly familiar with it, yet control of the prothrombin time was not perfect. In 7 of the 40 patients the prothrombin time was noted in retrospect to have been less than twice the control values on more than one occasion. None of these seven patients, however, developed deep vein thrombosis. In contrast, there is no difficulty in controlling the dose of dextran. In addition, dextran 70 in double the dose used in the present study has no effect on

clotting-time or bleeding-time in man (Nilsson and Eiken, 1964). The optimum dose of dextran 70 is not yet known. In view of the high proportion of thrombi which are detectable on the day after operation it is likely that the prophylactic effect is mainly achieved by the dextran given during operation and it may not be necessary to continue administration afterwards.

The mechanism of the protective effect of dextran 70 may not depend exclusively on suppression of platelet activity. Infusion of dextran 70 expands the plasma volume, thereby increasing the cardiac output and venous blood flow. It seems that increased venous flow cannot alone account for the prophylactic effect since similar protection against experimental venous thrombosis is not afforded by albumin in equivalent oncotic dosage (Gruber and Bergentz, 1966). Increased venous flow may, however, be a contributory factor. In addition, dextran is known to coat vascular endothelium (Bloom *et al.*, 1964) and has also recently been shown to modify fibrin polymerization both in animals (Gollub and Schaefer, 1968) and in man (Dhall *et al.*, 1970). The relative importance of these factors in the effectiveness of dextran 70 as an antithrombotic agent is not known, but together they serve to emphasize the theoretical attraction of using the substance in clinical prophylaxis.

Finally, though the place of dextran 70 as a prophylactic agent against postoperative thigh and leg venous thrombosis is established, and many will prefer for simplicity and safety to use it instead of anticoagulants, it is desirable to compare its effectiveness with that of efficient anticoagulation begun before operation. Such a controlled trial is currently in progress.

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