Venous thromboses in myocardial infarction

Comparison in heparin dosage

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A prospective trial of the incidence of deep venous thrombosis as detected by the ¹²⁵I-labelled fibrinogen technique was performed in patients with acute myocardial infarction. One hundred and sixteen patients completed the trial and were randomly allocated full therapeutic heparin dosage intravenously (63 patients), while control patients received 1,000 units of heparin daily. The incidence of venous thromboses in the control group was not significantly different from the therapeutic group (12.7% and 9.4%, respectively). The previously documented low incidence of clinical features of calf vein thrombosis was confirmed.

A high incidence of venous thromboses was shown in patients with cardiac failure (17%), and in this subgroup full anticoagulant dosage was associated with a significant reduction. The trial was terminated as no overall difference was apparent, and the incidence of venous thromboses was lower than in other studies where anticoagulants had not been used. The latter suggests that very low doses of heparin reduce the incidence without the risk of haemorrhagic complications. A further prospective trial with addition of a group receiving no heparin is presently being undertaken.

Over the past 12 years the technique of using radioactively labelled fibrinogen, with external scintillation counting, has been developed to detect venous thrombosis in the legs (Hobbs and Davies, 1960; Palko, Nanson, and Fedoruk, 1964; Atkins and Hawkins, 1965, 1968; Nanson *et al.*, 1965). Where an increased uptake of the isotope has occurred, phlebography has confirmed the presence of venous filling defects. The incidence of venous thromboses in patient groups studied has been shown to be higher than detected clinically, and the use of this method has become widely accepted because of its simplicity and diagnostic accuracy (Kakkar, Flanc, and Tsapogas, 1968; Flanc, Kakkar, and Clarke, 1968; Negus *et al.*, 1968; Kakkar *et al.*, 1970a, b; Lambie *et al.*, 1970).

The management of myocardial infarction is usually characterized by a period of relative immobility, and may be complicated by the development of venous thromboses and pulmonary thromboembolic disease. One of the major indications for the use of anticoagulants in the management of acute myocardial infarction has been in the prevention of venous thrombosis (Ebert, 1972).

Recent reports using radioactively labelled fibrinogen have shown a much higher incidence than had previously been recognized (Murray *et al.*, 1970; Maurer, Wray, and Shillingford, 1971; Maurer, 1970; Nicolaidis *et al.*, 1971).

We have studied the incidence of venous thromboses in the legs of patients with acute myocardial infarction, and an attempt has been made to determine whether anticoagulation affects this incidence.

Patients and methods

The patients studied in the trial were all admitted to the Coronary Care Unit of the Alfred Hospital where a diagnosis of acute myocardial infarction was confirmed by standard electrocardiographic criteria and serum enzyme changes (aspartate aminotransferase and lactate dehydrogenase). Fifty-five patients with an acute myocardial infarction were excluded as they either had contraindications to the use of anticoagulants or had received them before admission and so could not be randomized. Eighteen patients were excluded because of cardiogenic shock on admission, 11 because of the insertion of a transvenous pacemaker, and 7 because the infarct had occurred more than 48 hours previously. Twenty-three patients were not included because of technical problems with the scintillation counter or supply of ¹²⁵I, and one as the patient had only one leg.

A number of patients were initially randomized and later withdrawn from the study because the clinical

Received 6 October 1972.

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TABLE 1 Comparison of control and treated groups

	Control	Anticoagulated
Sex { Male	50	45
Female	13	7
Mean age (yr)	56.5	53.8
Mean weight (kg)	74.1	73.6
Mean surface area (m ²)	1.77	1.81
Mean admission time from probable infarction (hr)	7.9	9.5

diagnosis of myocardial infarction was not substantiated. Seven patients who entered the trial were subsequently excluded; anticoagulation was stopped in 3 because of bleeding problems, and was started in 4 patients, 3 because the attending physician thought it necessary and 1 because of a systemic embolus to the femoral artery.

One hundred and sixteen patients who were randomly allocated anticoagulation completed the trial, there being 63 control patients of whom 50 were male, and 53 fully anticoagulated patients of whom 46 were male. When compared for age, weight, surface area, and time from presumed infarction (as judged by the time of the most severe pain) to admission to the coronary care unit the two groups were similar (Table 1).

Patients allocated to the treatment group were given a loading dose of 5,000 units of heparin intravenously, followed by an infusion of 20,000 units, 12-hourly for 48 hours, the dosage being adjusted to maintain a whole blood clotting time of greater than 30 minutes and less than 90 minutes. Warfarin sodium in an adequate dosage to keep the prothrombin index between 10 and 35 per cent was started on admission. Control patients were given an intravenous infusion of 500 units of heparin, 12-hourly for 48 hours, or longer if the intravenous drip was left *in situ*. No control patient had a prolonged whole blood clotting time.

On admission, the patients were given 85 mg sodium iodide intravenously to reduce the uptake of radioiodine by the thyroid gland. Potassium iodide, 60 mg twice daily, was continued subsequently for 3 weeks.

One hour after the sodium iodide was given, 200 μ Ci of ¹²⁵I-labelled fibrinogen was given intravenously. The fibrinogen was derived from a selected pool of donors from the Australian Red Cross Blood Bank, and labelled with ¹²⁵I (obtained from the Radio Chemical Centre, Amersham) by the jet-iodination technique described by McFarlane (1963).

Using a portable scintillation counter, counts were made daily over the praecordium and 8 positions on each leg for 7 to 10 days, the legs being raised at 15° for 5 minutes before counting. Leg counts were expressed as a percentage of the praecordial count and referred to as the percentage uptake (Negus *et al.*, 1968). A difference of more than 15 per cent between identical positions on each leg or between points over the calf was the criteria for the diagnosis of venous thrombosis (Negus *et al.*, 1968). Daily examination for clinical signs

of venous thrombosis was undertaken. Active leg exercises were performed under the supervision of the nursing staff during waking hours, and the patients were discouraged from crossing their legs.

On admission to the coronary care unit assessment was made as to whether or not the patient was in cardiac failure, based on the presence of a third heart sound, basal moist sounds not clearing on coughing, or the appearance of radiological evidence of pulmonary venous congestion. The patients who developed cardiac failure had greater peak serum enzyme levels with the mean serum aspartate aminotransferase level being 284 Reitman-Frankel units compared with 183 Reitman-Frankel units in patients with no cardiac failure. The same pattern was noted with serum LDH levels.

The incidence of venous thrombosis in patient groups and subgroups was compared using the χ^2 test corrected for continuity.

Results

Of the 116 patients who completed the study period, 13 showed an increased uptake as evidence of deep venous thrombosis, an overall incidence of 11.2 per cent. The incidence in the 63 control patients was 12.7 per cent (8 patients), compared with 9.4 per cent (5 patients) of the 53 who were anticoagulated; this difference was not statistically significant (Table 2). There were no apparent differences as to age, sex, surface area, or time from infarction to admission between those developing thromboses and the overall group.

Cardiac failure was present in 22 patients in the control group, of whom 27 per cent developed venous thrombosis (6 patients), while in 20 patients who were anticoagulated none developed venous thromboses (Table 3). When cardiac failure was not present the incidence was 5 and 15 per cent, respectively (Table 4). Only the difference in the incidence in patients with cardiac failure was statistically significant ($P < 0.05$).

The length of confinement to bed which ranged from 2 to 10 days after admission did not affect the incidence of thrombosis. Five thromboses were transient lasting less than 48 hours, with the remaining 8 persisting up to 10 days (Table 5). Seven

TABLE 2 Overall incidence of venous thromboses

	No. of patients	Venous thromboses	Per cent incidence
Control (heparin, 1,000 units daily)	63	8	12.7
Anticoagulated	53	5	9.4

χ test: not significant ($P > 0.5$)

TABLE 3 Incidence of venous thromboses in patients in cardiac failure

	No. of patients	Venous thromboses	Per cent incidence
Control (heparin 1,000 units daily)	22	6	27
Anticoagulated	20	0	0
Total	42	6	14.3

χ^2 test: ($P < 0.05$).

TABLE 4 Incidence of venous thromboses in patients not in cardiac failure

	No. of patients	Venous thromboses	Per cent incidence
Control (heparin, 1,000 units daily)	41	2	5
Anticoagulated	33	5	15
Total	74	7	9.5

χ^2 : not significant ($P > 0.1$).

TABLE 5 Venous thromboses

	Control	Anticoagulated
Sex { Male	7	4
Female	1	1
Mean age (yr)	60.5	51.6
Mean weight (kg)	71.4	81.4
Mean surface area (m ²)	1.79	1.89
Mean admission time from probable infarction (hr)	8.0	16.7
Confined to bed (dy)	2-10	4-8
Transient thromboses	3	3

patients had thromboses in both legs, 1 in the left leg, and the remaining 5 in the right leg. All thromboses were confined to the calf region, none propagating to the popliteal vein, and there were no cases of clinical pulmonary embolism. No alteration was made to the anticoagulant therapy upon the detection of a raised uptake of isotope.

A history of varicose veins was obtained from 8 patients and 2 of these developed venous thrombosis, one being bilateral and the other being present in the right leg. Only one patient, a 58-year-old woman, who was allocated to the control group had

a past history of deep venous thrombosis; this patient had also suffered a pulmonary embolus. She was not in cardiac failure, and developed no evidence of venous thrombosis on this occasion.

Of the 13 patients with venous thrombosis, only 3 had clinical signs, one having an increased uptake of fibrinogen 24 hours before calf tenderness was elicited.

Three patients in the series died while still in the hospital, 1 from a further myocardial infarction on the 13th day, 1 from progressive cardiac failure associated with an acute ventricular septal defect, and the third from severe cardiac failure of long standing. The latter patient, who was in the control group, had a history of calf pain one week before admission, and died on the seventh day several hours after recurrence of chest pain. Necropsy confirmed recent myocardial infarction in all 3 patients, and pulmonary embolism and venous thrombosis of the deep veins in the right calf was present in the third patient. This was presumably not detected as the thrombus was probably present 7 days before labelled fibrinogen was given, and was thus not incorporated into the thrombus.

Discussion

The incidence of deep thrombosis and acute myocardial infarction as determined by the ¹²⁵I-labelled fibrinogen technique in patients not receiving anticoagulants has been reported to be 34 per cent by Murray *et al.* (1970), 37 per cent by Maurer *et al.* (1971), and 38 per cent by Nicolaides *et al.* (1971). Pooling the results of these groups gives an incidence of 51 thromboses in 138 patients, i.e. 37 per cent. Nicolaides *et al.* (1971), in a small series of 13 patients, showed a reduction in incidence with the use of full dose anticoagulants to 5.5 per cent. In the presently reported series, we found an incidence of 9.4 per cent in a group of 53 receiving full dosage anticoagulants. It appears that the incidence of venous thrombosis is significantly reduced by the use of standard therapeutic doses of anticoagulants.

In preparing a protocol for the current trial, it was decided to give control patients 500 units of heparin intravenously 12-hourly, as was the current practice at the Alfred Hospital in patients receiving dextrose infusion, because it was thought that it would reduce the incidence of infusion obstruction. At the onset of the trial, it was not felt that the small dosage of heparin used would influence the results. The incidence in the control group was not found to be significantly different from those fully anticoagulated, thus implying that small doses of heparin appear as effective as the full therapeutic regimen in the prevention of venous thrombosis.

Low dosage heparin has been shown in postoperative surgical patients to reduce the frequency of deep venous thrombosis (Sharnoff, Kass, and Mistica, 1962; Sharnoff, 1966; Sharnoff and DeBlasio, 1970; Kakkar *et al.*, 1971; Gordon-Smith *et al.*, 1972), though these series used at least 10,000 units of heparin daily without alteration of whole blood clotting time or thrombin clotting time.

The mechanism of action of low dosage heparin remains unknown at the present time, though several theories have been postulated. In ischaemic heart disease, McDonald and Edgill (1957) have shown increased platelet stickiness, and Slack *et al.* (1964) found that lipoprotein lipase activity was significantly lower in this group. Negus, Pinto, and Slack (1971) and Ham and Slack (1968) demonstrated that intravenous heparin in small dosage (1–10 units per kg) reduces the increased postoperative platelet adhesiveness, this being accompanied by a rise in lipoprotein lipase activity. Yin and Wessler (1970) have suggested that heparin enhances the activity of a potent naturally occurring inhibitor to activated factor X, without altering the whole blood clotting time.

Nicolaides *et al.* (1971), in a small group of patients with acute myocardial infarction, suggest that there is an increased incidence of venous thromboses in those patients who are 'severely ill'. In the current series no significant difference in the incidence of venous thromboses was found when patients with and without failure were compared ($P > 0.5$). However, when the patients in cardiac failure are subdivided into those receiving full and low dose anticoagulation, a significant difference appears in favour of the full dosage group. Among the patients without cardiac failure, there was an increased incidence of venous thrombosis in those patients receiving anticoagulants (15% compared with 5%): this figure was not significant. Of the 5 patients in this group receiving anticoagulants, 4 were the only patients to show an increased uptake on the first day of counting, and it could be postulated that these 4 patients were laying down thrombus at the time of admission, so that labelled fibrinogen was incorporated before the therapeutic effect of the anticoagulant regimen. Analysis of these 4 patients showed no apparent differences in age, surface area, or time from infarction to admission from the remainder of the groups; however, all were male patients. If these 4 patients are excluded from the overall series, then there is a reduction in incidence in the anticoagulated patients to 2 per cent (1 patient out of 49), and the apparent anomaly of anticoagulants increasing venous thrombosis in patients without cardiac failure is eliminated.

In all our cases, thrombus was detected only in

the calf and none spread to the popliteal or femoral veins. No case of clinical pulmonary embolism was observed. Most thrombi were present in the right leg, which is in disagreement with the observation of Atkins (1946) that the thrombus is more likely to originate in the left leg.

Kakkar *et al.* (1970a) showed a high incidence of venous thromboses in postoperative patients who had had a previous leg vein thrombosis, and a 100 per cent incidence in those with a previous history of pulmonary embolism. In our study only a single patient had a history of venous thrombosis and pulmonary embolism, and she did not show any increased uptake of isotope at this admission, even though she was randomized to the control group.

The results of the current study suggest that very low dose heparin provides the same benefit as full dose anticoagulation in the prophylaxis against venous thrombosis in patients with acute myocardial infarction who are not in cardiac failure. Confirmation of these data will allow the benefits of low dose heparin therapy to be extended to those in whom anticoagulants have previously been contraindicated. In the presence of cardiac failure it appears that some benefit is achieved, but in the current small series, full dosage heparin was more effective.

As fibrinogen is derived from pooled sera, there is a risk of transmission of the virus of serum hepatitis, and Laiwah *et al.* (1970) reported two cases of hepatitis with positive Australia antigen five months after the injection of ^{125}I -labelled fibrinogen. We have used fibrinogen from a carefully screened group of donors in order to reduce this risk, and no case of hepatitis has occurred among the patients studied in the present series or among approximately 500 other studies at the Alfred Hospital. We have detected no complications with the usage of the labelled fibrinogen technique.

This trial was concluded after 116 patients had been studied, as no statistical difference could be shown in the incidence of deep venous thrombosis in the group receiving full dosage compared with the group receiving low dosage heparin. A further prospective trial is being undertaken in acute myocardial infarction comparing the use of no anticoagulants, 1,000 units of heparin intravenously daily, and full therapeutic dosage of heparin, on the incidence of venous thromboses.

We wish to acknowledge the very valuable assistance we received from Mr. D. S. Rosengarten, F.R.A.C.S., and the members of the nursing and technical staff.

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