PAPERS AND ORIGINALS

Prophylaxis of Postoperative Leg Vein Thrombosis by Low dose Subcutaneous Heparin or Peroperative Calf Muscle Stimulation: A Controlled Clinical Trial*

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Summary

In a randomized, controlled clinical trial of two methods of preventing postoperative leg vein thrombosis patients undergoing major surgery were divided into three groups. One received intermittent electrical calf muscle stimulation during surgery, the second subcutaneous heparin calcium 5000 IU every eight hours for six days, and the third no specific prophylaxis. Leg vein thrombosis was detected by the ^{125}I-fibrinogen uptake test.

Neither method was effective in patients undergoing open bladder or prostatic surgery. Stimulation did not reduce the incidence of leg vein thrombosis in patients with malignant disease undergoing laparotomy, but heparin calcium was highly successful in this group ($P < 0.001$). When the laparotomy was for a benign condition, however, both heparin calcium ($P < 0.001$) and stimulation ($P < 0.01$) were effective.

Introduction

Pulmonary embolism kills four or five out of every thousand patients operated on (*British Medical Journal*, 1973). Most emboli originate in the legs (Browse *et al.*, 1974) and leg exercises and early ambulation have long been accepted methods of prophylaxis. The last 15 years, however, have seen the introduction of various additional regimens, when assessment has been facilitated by the radioactive fibrinogen uptake test (Kakkar *et al.*, 1970).

We designed a trial to compare two additional methods—low-dose subcutaneous heparin (Kakkar *et al.*, 1972) and electrical calf muscle stimulation (Doran, 1971)—with standard physiotherapy.

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Patients and Methods

All patients aged over 40 undergoing a major general surgical operation for which they were expected to be in hospital for at least a week were eligible to enter the trial (provided consent to the fibrinogen uptake test was obtained). No patient was excluded on the grounds of pre-existing cardiorespiratory disease, peripheral vascular disease, varicose veins, or a previous history of thrombosis, but for technical reasons patients undergoing thyroidectomy, left mastectomy, and peripheral arterial reconstruction were not studied. Instruction in leg exercises was given to all patients, who were also encouraged to walk as soon as possible after operation.

Randomization into three groups was by the month of birth. Patients born in the first four months of the year had intermittent electrical calf muscle stimulation during surgery (stimulator treatment); those born in the second four months received low-dose subcutaneous heparin calcium (Calciparine Sous-cutanée), and those born during the last four months had leg exercises only (controls).

The apparatus used for electrical calf muscle stimulation was the Thrombophylactor (Rank Precision Industries Ltd.), which delivers an interrupted direct current of 50 milliseconds duration every five seconds, each pulse being automatically reversed in polarity to avoid tissue ionization. The voltage is adjustable on the control panel to cause calf muscle contraction without affecting thigh muscles. The electrodes were strapped to the legs, one on the upper calf and the other above the ankle, before induction but not switched on until the endotracheal tube was in position. At the end of the operation the stimulator was turned off when the tube was removed. We were not then aware of the potential hazard of the failure of the output transistors when surgical diathermy was used concurrently (D.H.S.S., 1974), but no skin burns were caused by the stimulator.

Heparin calcium was administered subcutaneously into the anterior abdominal wall in a 0·2-ml dose containing 5000 IU, the first dose two hours before operation and then every eight hours until the end of the sixth postoperative day or until the patient was fully mobile, whichever was the longer.

The fibrinogen uptake test was performed on all patients. The thyroid was blocked with potassium iodide 90 mg given by mouth or

intravenously before surgery and then daily for 21 days. Immediately after the operation 1 ml of solution containing about 100 μCi of ^{125}I-fibrinogen was injected intravenously. A Pitman 235 localization monitor was used to measure the radioactivity at 10-cm intervals from the upper thighs to the lower calves, and this was expressed as a percentage of the heart count. The measurements were taken the day after operation and then on alternate days (or daily if indicated) up to the seventh day. The criterion for the diagnosis of a deep vein thrombosis was a difference of 20% or more in a leg count on two or more occasions. When the graphs of the leg counts were interpreted, however, the day of onset of the thrombosis was regarded as the first occasion on which a rise in the count was discovered, even if the first rise was not as much as 20%. A minor thrombosis was defined as a 20% rise in scintillation count at one or two points below the knee, whereas a major thrombosis was defined as one which extended or occurred above the knee (and was therefore of potential clinical significance).

Results

Altogether 295 patients entered the trial. Of these 14 were withdrawn because of failure to observe the protocol, four because they died within four days, and four because heparin prophylaxis was stopped after reactionary haemorrhage. The results of 273 operations were therefore analysed, and 118 legs in 84 patients showed positive results to fibrinogen uptake tests.

Neither method of prophylaxis reduced the incidence of leg vein thrombosis below control level in patients undergoing bladder, prostate, and miscellaneous surgery (there were only 20 patients in the miscellaneous group, and two in each prophylaxis group suffered a venous thrombosis) (table I).

In the remaining 194 patients, all of whom had a laparotomy, the heparin calcium group showed a significantly lower incidence of both minor and major venous thrombosis (7·3% and nil respectively compared with 23·6% and 20·2% in the controls). The use of the stimulator did not effect the rate of minor thrombosis, but the incidence of major thrombosis was significantly lower at 4·0%. The 194 patients who had a laparotomy were divided into those with and those without malignant disease (table II). In patients with malignant disease heparin calcium proved effective as a preventive agent, but the stimulator was ineffective. When a laparotomy was performed for benign disease heparin calcium significantly reduced the incidence of both major and minor venous thrombosis, whereas the stimulator prevented major thromboses alone.

Altogether 34·7% of thromboses in the control group first appeared later than the first day after operation (table III). A similar pattern was apparent in the stimulator group, but in the heparin series 64·3% developed after the first postoperative day, which was significantly different from the control ($\chi^2 = 4·29$; $P < 0·05$).

Clinically diagnosed leg vein thromboses and pulmonary emboli were uncommon, there being one thrombosis and one non-fatal embolus among the controls and one non-fatal embolus in the heparin calcium group.

Four patients receiving heparin prophylaxis developed reactionary haemorrhages great enough to warrant blood transfusion and cessation of therapy, but these could have arisen by chance. No problems were encountered with primary haemorrhage during operation.

TABLE I—*Results of Prophylaxis in Three Groups of Patients. Results are Numbers (%) of Patients who developed Deep Vein Thrombosis (D.V.T.)*

	All Laparotomies	Significance of Difference from Controls (χ^2 P)	Bladder and Prostate Operations*
		Controls	
No. of patients	89		32
Minor D.V.T.	21 (23·6)		8 (25·0)
Major D.V.T.	18 (20·2)		3 (9·4)
Total D.V.T.	39 (43·8)		11 (34·4)
		Stimulator	
No. of patients	50		23
Minor D.V.T.	12 (24·0)	N.S.	5 (21·7)
Major D.V.T.	2 (4·0)	6·84; <0·01	3 (13·0)
Total D.V.T.	14 (28·0)	3·4 ; <0·10	8 (34·8)
		Heparin Calcium	
No. of patients	55		24
Minor D.V.T.	4 (7·3)	4·40; <0·05	7 (29·2)
Major D.V.T.	0	12·71; <0·001	1 (4·2)
Total D.V.T.	4 (7·3)	21·68; <0·001	8 (33·3)

* No differences from controls in either of the other groups were significant.

Discussion

Heparin administered subcutaneously in doses low enough not to affect the whole blood clotting time is highly effective in the

TABLE II—*Results of Prophylaxis in Three Groups of Patients undergoing Laparotomy for Benign or Malignant Disease. Results are Numbers (%) of Patients who developed Deep Vein Thrombosis (D.V.T.)*

	Laparotoy for Benign Disease	Significance of Difference from Controls (χ^2 P)	Laparotomy for Malignant Disease	Significance of Difference from Controls (χ^2 P)
		Control		
No. of patients	57		32	
Minor D.V.T.	13 (22·8)		15 (46·9)	
Major D.V.T.	7 (12·3)		4 (12·5)	
Total D.V.T.	20 (35·1)		19 (59·4)	
		Stimulator		
No. of patients	37		13	
Minor D.V.T.	6 (16·2)	N.S.	6 (46·2)	N.S.
Major D.V.T.	0	4·90; <0·05	2 (15·4)	N.S.
Total D.V.T.	6 (16·2)	6·72; <0·01	8 (61·5)	N.S.
		Heparin Calcium		
No. of patients	34		21	
Minor D.V.T.	3 (8·8)	2·87; <0·10	1 (4·8)	10·67; <0·01
Major D.V.T.	0	4·52; <0·05	0	2·83; <0·10
Total D.V.T.	3 (8·8)	11·04; <0·001	1 (4·8)	16·10; <0·001

TABLE III—*Day after Operation when Onset of Deep Vein Thrombosis (D.V.T.) occurred, as detected by Fibrinogen-uptake Test, in 118 Legs*

Day of onset of D.V.T. :	1st	2nd	3rd	4th	5th-7th	Total
No. (%) of control legs	47 (65·3)	4 (5·6)	14 (19·4)	7 (9·7)	0	72 (100)
No. (%) of stimulated legs	20 (62·5)	6 (18·8)	2 (6·3)	2 (6·3)	2 (6·3)	32 (100)
No. (%) heparin-treated legs	5 (35·7)	1 (7·1)	6 (42·9)	0	2 (14·3)	14 (100)

prophylaxis of postoperative leg vein thrombosis (Kakkar *et al.*, 1972; Gordon-Smith *et al.*, 1972; Lahnborg *et al.*, 1974). The obstacle to the universal acceptance of heparin prophylaxis has been the fear of haemorrhage resulting from interference with the clotting mechanisms. Numerous alternative methods have been designed to promote venous return from the legs during operation. The best of these (which include leg bandaging, leg elevation, intermittent ankle movements, rhythmic calf muscle stimulation, and pneumatic compression) seem to be the last two, both of which in controlled clinical trials have reduced the incidence of leg vein thrombosis (Browse and Negus, 1970; Roberts and Cotton, 1974).

Our results show that a regimen of low-dose subcutaneous heparin is an effective prophylaxis for patients undergoing laparotomy. Electrical calf muscle stimulation was nearly as effective in these patients but only when the operation was for a benign condition. That this may have been due to the different duration of prophylaxis is suggested by the work of Gordon-Smith *et al.* (1972), who reported that heparin administration confined to the 24 hours during and after operation was ineffective in patients suffering from malignant disease.

It is generally thought that leg vein thrombi originate during operation but we detected only two-thirds of the episodes of thrombosis in the control group on the first day after operation. The remainder apparently formed on the second day or later and prophylaxis confined to the period of the operation could not be expected to prevent them.

Though the electrical method is safe and without side effects (so long as the apparatus is adequately designed) and may be the method of choice in patients undergoing laparotomy for benign disease it seems to be a poor alternative to heparin for routine use.

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Maternal Serum α-Fetoprotein Levels in Multiple Pregnancy

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Summary

Maternal serum α-fetoprotein (AFP) levels were higher in 10 twin pregnancies and one triplet pregnancy than in 22 control singleton pregnancies matched for maternal age, parity, and the time of gestation at which the serum sample was taken. In twin pregnancies the average AFP levels were double those found in singleton pregnancies and the level in the triplet pregnancy was even higher. Raised maternal serum AFP values due to multiple pregnancy should not cause unnecessary amniocentesis in the diagnosis of anencephaly or spina bifida if an ultrasound investigation is routinely performed first.

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Introduction

Maternal serum α-fetoprotein (AFP) levels are abnormally high with anencephaly and spina bifida (Wald *et al.*, 1974; Brock *et al.*, 1974), and their measurement may be useful in screening pregnant women for these abnormalities. There is, however, a lack of information on other factors which can cause high AFP levels. It has been suggested that the fetus is the source of the increased maternal serum AFP in pregnant women (Seppälä and Ruoslahti, 1972), and we therefore examined the relation between multiple pregnancy and maternal serum AFP levels early in pregnancy.

Methods

In Oxford, where a large prospective survey of the outcome of pregnancy has been in progress for nearly two years, about 40 000 antenatal serum samples have been stored routinely at −40°C. From this survey 10 twin pregnancies and one triplet pregnancy were each matched with two control singleton pregnancies for age of mother (within three years), parity, and time of gestation at which a serum sample was obtained (within 17 days). Sera were taken at or before 20 weeks gestation in all the multiple pregnancies except one, which was taken at 25 weeks. No patient had had a previous child with a neural tube defect, and all the pregnancies had resulted in normal infants. None of the women with a twin pregnancy or their controls had a past history of abortion. The patient with the triplet pregnancy (case 11) had had three previous abortions and was matched with two control patients, each with two previous abortions. Sera from these 33 pregnant women were assayed for AFP using a double-antibody radioimmunoassay (Brock *et al.*, 1974). All the reagents used in the assay were from the same batch, and the estimations were performed without knowledge of details of the women or their pregnancies. Each sample was assayed three times.