S.D. 9) above the knee. The size of the largest natural variations suggests that the difference of 20% as a diagnostic determinant is better than the level of 15%.

In general, these findings suggest that the ^{125}I-fibrinogen test, even without supporting evidence of phlebography, can lead to false diagnoses of D.V.T. As techniques of prophylaxis become more successful it becomes more important that diagnosis is totally unambiguous. Furthermore, it becomes progressively more important for trial results to be compared. Hence, clinical trials should take some account of the value of a standard method of both monitoring and subsequent analysis, possibly incorporating the following principles: the precordial reading should always be made with the subject fully recumbent; all readings should be corrected for daily variations in the background; patients should be monitored every day for not less than six days and readings should be made at 2-in (5·1-cm) intervals; the readings should be corrected for the possibilities of instrument mishandling; in reaching a diagnosis readings at each position on the leg should be compared (after correction for background and probe placement) with the immediate postoperative scan. A difference of 20% or more at any position on two or more consecutive days should be taken to indicate a thrombosis.

TABLE V—*Diagnostic Percentage Uptake Counts for Patient in Table I after Correction for Background and Probe Mishandling*

Position	After Operation	Day 1	Day 2	Day 3
1	36	58	21	23
2	28	38	21	22
3	26	18	21	23
4	26	20	21	25
5	30	26	21	26
6	28	18	28	22
7	28	20	28	21
8	26	20	23	20
9	24	15	24	22
10	24	21	26	20
11	24	20	23	20

To indicate the effectiveness of this technique the readings for the patient in table I were corrected according to these guidelines. It was discovered that the readings on day 2 had been taken only minutes after the patient had returned to the ward after radiotherapy. The corrected readings are shown in table V. It was taken (perhaps incorrectly) that this patient, though developing a small clot in position 1 on day 1, did not clot her entire leg on day 2. Unfortunately phlebography was not performed.

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References

1 Flanc, C., Kakkar, V. V., and Clarke, M. B., *British Journal of Surgery*, 1968, 55, 742.
2 Negus, D., *et al.*, *British Journal of Surgery*, 1968, 55, 835.
3 Kakkar, V. V., *et al.*, *Lancet*, 1970, 1, 540.
4 Lambie, J. M., *et al.*, *British Medical Journal*, 1970, 2, 142.
5 Lambie, J. M., *et al.*, *British Medical Journal*, 1970, 2, 144.
6 Browse, N. L., and Negus, D., *British Medical Journal*, 1970, 3, 615.
7 Rosengarten, D. S., and Laird, J., *British Journal of Surgery*, 1971, 58, 182.
8 Milne, R. M., *et al.*, *Lancet*, 1971, 2, 445.
9 Sabri, S., Roberts, V. C., and Cotton, L. T., *British Medical Journal*, 1971, 3, 82.
10 Sabri, S., Roberts, V. C., and Cotton, L. T., *British Medical Journal*, 1971, 4, 394.
11 Hills, N. H., *et al.*, *British Medical Journal*, 1972, 1, 131.
12 Gordon-Smith, I. C., *et al.*, *Lancet*, 1972, 1, 1133.
13 Bonnar, S., and Walsh, J., *Lancet*, 1972, 1, 614.

Failure of Low-dose Heparin to Improve Efficacy of Peroperative Intermittent Calf Compression in Preventing Postoperative Deep Vein Thrombosis

V. C. ROBERTS, L. T. COTTON

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Summary

The possible benefits of adding a low-dose heparin regimen to the technique of peroperative intermittent calf compression for preventing deep vein thrombosis (D.V.T.) were assessed in a randomized trial in 84 surgical patients. The efficacy of peroperative intermittent calf compression was not enhanced by a low-dose heparin regimen, but neither was it worsened. Age, weight, duration, operation, and malignant disease did not affect the relative effectiveness of the two regimens of prophylaxis. The results confirmed that venous stasis is the principal cause of D.V.T.

Department of Biomedical Engineering, King's College Hospital Medical School, London SE5 8RX

V. C. ROBERTS, PH.D., M.I.E.E., Lecturer

L. T. COTTON, M.CH., F.R.C.S., Consultant Surgeon and Director of Department

Introduction

Over the past five years considerable advances have been made in the search for an effective method of preventing postoperative deep vein thrombosis (D.V.T.) and its sequelae. Latterly, successful methods have fallen into two classes—those using low-dose subcutaneous heparin designed to prevent thrombus formation, and those using physical techniques designed to prevent venous stasis. It has long been argued that the principal causes of venous thrombosis are (*a*) a change in the biochemistry of the blood, (*b*) physical damage to the lining of the vessel wall, and (*c*) stasis of blood within the veins. Little can effectively be done to measure or control *b*, which perhaps explains the concentrated effort that has been expended on the remaining two.

In the belief that venous stasis is the principal initiating factor of venous thrombosis we have concentrated our efforts on physical methods of stimulating the venous flow. We have been able to show the efficacy of a very simple method of prophylaxis using intermittent calf compression during operation. This technique, which was derived from extensive haemodynamic investigations,[1 2] reduces the incidence of postoperative thrombosis by up to 90%.[3 4] Despite its apparent success and evident simplicity, however, we have been unable to prevent totally postoperative thrombosis with this method. One possible reason

for this is that until now the method has been applied only during the operation and not during the postoperative phase.

Concurrently with our research into physical methods of prophylaxis the use of low-dose subcutaneous heparin has been gaining popularity and has proved to be as effective as our method in preventing thrombosis. Successful heparin regimens are those extending for a full seven days after operation and which might be expected to prevent the late-occurring thromboses that our physical method leaves untouched. A combination of the two methods of prophylaxis might be expected, therefore, to produce a dramatic abolition of D.V.T. by effectively dealing with the venous stasis which occurs during operation and the biochemical changes which occur subsequently in the blood. Accordingly we conducted a trial to assess the benefits of adding a low-dose heparin regimen to our technique of intermittent calf compression as a method of preventing postoperative D.V.T.

Patients and Methods

Patients over the age of 40 undergoing routine surgery lasting for longer than 30 minutes were entered consecutively into the trial. The only patients excluded were those undergoing leg surgery (including arterial reconstruction), thyroid surgery, or left mastectomy. No exclusions were made on the grounds of operative position, thus patients were treated both supine and in the lithotomy position.

Patients were randomly assigned to one of two treatment regimens. All patients were subjected to peroperative intermittent calf compression of both legs[4] using the BOC-Roberts Venous Flow Stimulator. The calf compression started when the patient was placed on the operating table and stopped when the patient was removed from the table. In one group of patients an additional low-dose heparin regimen was used; 5000 units of sodium heparin were given subcutaneously one hour before operation and then every 12 hours for seven days. The other group of patients received 1-ml injections of saline before operation and twice daily for seven days. All injections were given in the thigh.

Comparative Incidence of Thrombosis Using Two Diagnostic Regimens: Diagnosis 1 was Based on Two Consecutive Rises in Percentage Count, Diagnosis 2 was Based on Three Consecutive Rises in Percentage Count. Results are Numbers of Patients with D.V.T. out of Total in Group

Group	Diagnosis 1		Diagnosis 2	
	No.	%	No.	%
		Patients		
Heparin	10/39	25·6	5/39	12·8
Placebo	8/45	17·8	3/45	6·7
		Legs		
Heparin	12/78	15·4	5/78	6·4
Placebo	10/90	11·1	4/90	4·4

The ^{125}I test was used to diagnose D.V.T. To block the thyroids all patients received 100 mg sodium iodide either orally 24 hours before administration of ^{125}I fibrinogen or intravenously one hour before. Oral sodium iodide (100 mg) was continued daily for 28 days. All patients received an injection of 100 μCi of ^{125}I fibrinogen (Radiochemical Centre, Amersham) at least two hours before operation and the radioactivity was measured over the legs 30 minutes later—that is, before premedication.

The counting equipment used was the Pitman 235 isotope monitor. The patients were scanned according to a modification[5] of the method of Flanc *et al.*,[6] in which the machine is set to 100% with the patient fully supine and the counter over the precordium. Legs were raised 30° to the horizontal by placing the feet in a special portable stand and readings were taken every 2 in (5·1 cm) from ankle to groin (six readings on the calf and five on the thigh). The percentage of the count caused by background radiation was noted. Scans were made before operation, immediately after the patient was removed from the operating table, and for six days after operation.

CONTRIBUTING FACTORS

The role of obesity as a contributing factor to the incidence of D.V.T. was studied in both groups of patients. Each patient was weighed and had his or her height measured. They were then assigned a fat index of -1, 0, 1, or 2 depending on the weight: height ratio. These fat indices were derived from published tables of desirable weights for adults[7] after correcting for unclothed weight and height. Overlaps in the ranges of desirable weight in the published table were eliminated by averaging out the overlap and the assigned indices were then -1, small frame; 0, medium frame; 1, large frame; and 2, weight in excess of the large frame. As an example of the weight ranges used, a man 5 ft 10 in (178 cm) tall would be ascribed the following indices according to weight: 62·3-66·0 kg index -1; 66·1-70·5 kg index 0; 70·6-78·2 kg index 1; and >78·3 kg index 2.

To assess the possible contributory role of confinement to bed a note was made each day of whether the patient was confined to bed and whether he had an intravenous infusion.

Results

Eighty-four patients entered the trial, 39 in the heparin group and 45 in the placebo group. The diagnosis of deep vein thrombosis was based on the criteria suggested by Roberts[5] in which the immediate postoperative scan was used as a baseline. Readings were corrected daily for variations in background activity and probe misplacement. D.V.T. was diagnosed when the corrected percentage count at any position was observed on at least two consecutive days to be 20% or more greater than the reference reading taken at that position immediately after operation.

In the heparin-treated group 10 patients out of 39 (25·6%) developed deep vein thrombosis on these criteria. Of the 10 two developed thrombosis bilaterally, thus the incidence based on leg thrombosis was 15·4%. In the placebo group eight patients out of 45 (17·8%) developed deep vein thrombosis. Again two patients developed thromboses bilaterally, giving a leg incidence of 11·1%. There was no significant difference—that is, a P value <0·05—between these groups when assessed with the χ^2 test and applying Yates's correction.

SEX DISTRIBUTION

There were 14 men in both groups—35·9% of the heparin group and 31·1% of the placebo group. This difference was not significant. Four of the 10 (40%) patients on heparin who developed D.V.T. were men, as were two of the eight (25%) patients in the placebo group who developed D.V.T. Thus the sex of a patient did not contribute significantly to the likelihood of a thrombosis.

AGE AND LENGTH OF OPERATION

In the heparin group the mean age (±S.D.) was 57·3±9·6 years and the mean length of operation 98·9±38·6 minutes. The corresponding figures for the placebo group were 58·6±14·6 years and 84·5±43·3 minutes. These differences were not significant.

In the heparin group the mean age of those patients who developed D.V.T. was 61·9±11·3 years and of those who did not 55·7±8·6 years. The mean length of operation of those who developed D.V.T. was 106·4±24·8 minutes and of those who did not develop thrombosis 96·3±42·5 minutes. Though both the mean age and operative duration of those who developed D.V.T. were greater than those of patients without D.V.T. the differences were not significant.

In the placebo group the mean age of those who developed D.V.T. was 65·1±15·6 years and that of those who did not was 57·5±14·2 years. The duration of operation in those patients who developed D.V.T. was 81·6±33·8 minutes while in those without D.V.T. it was 85·1±45·4 minutes. Again the differences were not significant.

MALIGNANCY

In the group who were treated with heparin 14 had malignant disease, and of these four developed D.V.T. In the placebo group three patients had malignant disease and none developed D.V.T.

These figures confirm that intermittent compression is effective in preventing deep vein thrombosis in patients with malignant disease, but the figures do not show that the addition of a low-dose heparin regimen significantly worsens the effectiveness of prophylaxis.

OBESITY

The fat index in those who received heparin was $1\cdot2\pm1\cdot0$ and in those who did not $1\cdot1\pm1\cdot1$. Within the heparin group those who developed D.V.T. had a mean fat index of $1\cdot4\pm1\cdot0$ while in those who did not develop D.V.T. the index was $1\cdot1\pm1\cdot0$. In the placebo group those developing D.V.T. had a fat index of $1\cdot3\pm1\cdot4$ while those not developing D.V.T. had an index of $1\cdot0\pm1\cdot0$. These figures indicate a slight increase in tendency for the patients with higher fat indices to develop D.V.T., but the differences were not significant either between or within the two groups.

BED CONFINEMENT

Among patients who received heparin the mean duration of intravenous infusion was $2\cdot6\pm1\cdot9$ days while the mean duration of bed confinement was $2\cdot7\pm1\cdot7$ days. Of the 39 patients in this group only two had no infusion during the postoperative period. The mean duration of intravenous infusion in the patients in this group who developed D.V.T. was $3\cdot5\pm2\cdot9$ days and the mean confinement to bed $3\cdot0\pm1\cdot4$ days. In those who did not develop D.V.T. the mean duration of bed confinement was $2\cdot6\pm1\cdot8$ days and the mean duration of intravenous infusion $2\cdot2\pm1\cdot4$ days.

In the placebo group the intravenous infusion lasted a mean of $2\cdot9\pm1\cdot6$ days and bed confinement a mean of $2\cdot5\pm1\cdot6$ days. Those who subsequently developed D.V.T. had a mean infusion time of $3\cdot3\pm1\cdot9$ days and a mean bed confinement of $2\cdot8\pm2\cdot3$ days. In those who did not develop D.V.T. the corresponding figures were $2\cdot8\pm1\cdot6$ days and $2\cdot4\pm1\cdot5$ days.

These figures indicate that patients either confined to bed or tethered to an intravenous infusion were more likely to develop D.V.T., but the differences within or between the groups were not statistically significant.

COMPLICATIONS

There was no excessive postoperative bleeding in any patient, but there was considerable evidence of minor haematoma around the injection site in patients who had received heparin. None of the placebo group developed any haematoma at the injection site.

One patient in the heparin-treated group died on the eighth day after gastrectomy. There was no evidence to suggest that heparin had contributed significantly to the death, which was attributed to peritonitis. No evidence of excessive haemorrhage or pulmonary embolus was found at necropsy. This patient had, however, suffered a large calf vein thrombosis on the second day after operation and an apparently isolated iliofemoral thrombosis on the fifth and sixth days.

Discussion

Our results showed, disappointingly, that the effectiveness of peroperative intermittent calf compression in preventing postoperative D.V.T. is not enhanced by the addition of an apparently equally successful heparin regimen. This is surprising because the calf compression regimen is only applied during the operation and might be expected to be effective principally on the thromboses originating at the time of operation. The heparin regimen, on the other hand, spans a whole week and would be expected to be effective in preventing the later thromboses as well as the early ones. The implication behind these findings, however bizarre it might appear, is that both intermittent calf compression and the seven-day heparin regimen are dealing with similar thrombi—that is, those that originate at the time of operation. This implies that there is, within any group of patients, a large variation in the rate of development of thrombi from a few hours to several days. The use of calf compression alone prevents most of these thrombi from starting. The use of the seven-day heparin regimen alone prevents them from developing. This apparent variation in development time perhaps explains why shorter heparin regimens, covering only the early postoperative period, have proved less successful.

The high overall incidence of D.V.T. in this trial reflected the criteria used for diagnosis. If three consecutive readings of 20% or more over the reference baseline are taken as necessary for a positive diagnosis instead of two consecutive readings—that is, a thrombosis must appear for more than 24 hours to be considered positive—then the overall incidence of thrombosis falls. As can be seen from the table, the incidence (whether assessed on a patient or leg basis) is more than halved. The incidences in the second diagnostic group are similar to those found previously by us in assessing the use of peroperative intermittent calf compression. The differences in incidence found when using the two diagnostic criteria serve to support the plea[5] for a universally standardized method of diagnosis so that some rational comparison may be made between future clinical trials.

Conclusion

We have shown that the addition of a seven-day low-dose heparin regimen to our method of peroperative intermittent calf compression to prevent postoperative D.V.T. is valueless. Our findings confirm that the venous stasis which occurs during surgery is the principal cause of postoperative thrombosis and suggest that the best way of abolishing it is to extend our physical method into the postoperative period. This may seem potentially costly, but when compared with the other available methods this was found not to be the case,[8] and the prevention of venous stasis is the most potent prophylactic against D.V.T. available.

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References

[1] Roberts, V. C., *et al.*, *British Journal of Surgery*, 1972, **59**, 223.
[2] Roberts, V. C., and Cotton, L. T., in *Blood Flow Measurement*, ed. V. C. Roberts. London, Sector Publishing, 1972.
[3] Sabri, S., Roberts, V. C., and Cotton, L. T., *British Medical Journal*, 1971, **4**, 394.
[4] Roberts, V. C., and Cotton, L. T., *British Medical Journal*, 1974, **1**, 358.
[5] Roberts, V. C., *British Medical Journal*, 1975, **3**, 458.
[6] Flanc, C., Kakkar, V. V., and Clarke, M. B., *British Journal of Surgery*, 1968, **55**, 742.
[7] Documenta Geigy, *Scientific Tables*, 7th edn, p. 712. Macclesfield, Geigy Pharmaceuticals, 1970.
[8] Roberts, V. C., and Cotton, L. T., *Lancet*, 1974, **2**, 1272.