

Seasonal variation in the incidence of deep vein thrombosis*

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SUMMARY

Two double-blind controlled clinical trials of the effectiveness of prophylactic low dose subcutaneous calcium heparin (dose based on body weight) in the prevention of deep vein thrombosis (DVT) have been completed. The first was concerned with upper abdominal operations in 242 patients over 21 years of age, and the second with 50 patients presenting with a fracture of the neck of the femur. There was no increase in the incidence of bleeding or wound complications in the patients given heparin. In each trial, the incidence of DVT as diagnosed by ¹²⁵I-labelled fibrinogen was significantly reduced in the treated group.

The incidence of DVT in the control groups varied significantly during the period of the trials. The incidence was much higher in the cold half of the year than in the hot months.

In the first trial, this variation in incidence was directly correlated with the average temperature and the diurnal variation in temperature in the perioperative period. These results may help to explain the considerable variation in the incidence of postoperative DVT reported from various parts of the world, and also from within Australia.

In 1971 we began a double-blind controlled clinical trial of the efficacy of low dose subcutaneous heparin in preventing postoperative deep vein thrombosis. The stimulus for this study derived from the demonstration of the effect of small doses of heparin on platelet function in the postoperative patient (Ham and Slack, 1968; Ham, 1969; Ham and Lawrence, 1977) and the belief that it thus might reduce the incidence of DVT. In this trial heparin was found to be effective, and it was also found that the incidence of DVT in the control group was not constant, the frequency being much higher in the cold period of the year than in the hot months. A second similar trial was then carried out in patients with femoral neck fractures and the variation in incidence was confirmed. We present here evidence that these findings may have been due to seasonal or climatic factors.

Patients and methods

Patients: first trial

All patients over the age of 21 years presenting for elective upper abdominal surgery in one surgical unit were considered for inclusion in the trial. The patient was approached if there was none of the following contraindications: severe liver or renal disease, a bleeding tendency, anticoagulant therapy, possible pregnancy, iodine allergy, Jehovah's Witness faith, isotope monitor failure, or less than 3 days' notice in patients admitted more than 4 days preoperatively. If informed written consent was obtained, the patient was allocated a number which referred to a box of ampoules containing either calcium heparin 10 000 i.u./ml (Calciparine, Choay) or saline, as randomized by the hospital pharmacist. The actual contents were known by the pharmacist only.

The patients were given 0.01 ml/kg of solution (i.e. 100 i.u./kg of heparin in the treated group) by deep subcutaneous injection into the thigh or lower abdomen approximately 3 hours before surgery and then 12-hourly for 5 days postoperatively, or

until full ambulation was achieved, whichever was the longer.

The details of the patients and the operations performed are shown in Table I. All patients had nitrous oxide-oxygen muscle-relaxant general anaesthesia and the operating table was horizontal.

Diagnosis of DVT: Deep vein thrombosis was diagnosed by the ¹²⁵I-labelled fibrinogen uptake test (Negus et al., 1968; Kakkar et al., 1970; Pai and Negus, 1971). Approximately 100 µCi of ¹²⁵I-labelled fibrinogen (Radiochemical Centre, Amersham) was given immediately postoperatively. Commencing on the first day after operation the legs were scanned daily by one observer (J. C. L.) until 3 days after the last subcutaneous injection. A Pitman 235 isotope localization monitor was used. With the legs elevated, the heart count was adjusted to read 100 per cent. Counts taken at sites 5 cm apart (6 on the calf and 5 on the thigh) were read as percentages of the heart count. Deep vein thrombosis was diagnosed if the count at any position on the leg was 20 per cent higher than the count at an adjacent site or at the same position on the other leg and if this elevation persisted for 24 hours or more. If, during the course of following a patient, the precordial count fell to an unacceptable level and the patient was not fully ambulant, the dose of ¹²⁵I-labelled fibrinogen was repeated.

In the case of patients in hospital for more than 4 days before operation, a dose of 50 µCi of ¹²⁵I-labelled fibrinogen was given at least 3 days preoperatively and their legs were scanned daily and immediately before operation. There were 71 such patients, 2 of whom had a positive scan and were therefore excluded from the trial (Table II).

All patients were given sodium iodide 100 mg daily, either orally or intravenously, 1 day before and for 1 month after receiving ¹²⁵I-labelled fibrinogen.

Patients: second trial

All patients presenting to the Accident Centre, Prince of Wales Hospital, with a fracture of the neck of the femur were considered for inclusion in the trial. The contraindications to inclusion were the same as in the first trial, and the method of randomization was also the same.

If informed written consent was obtained, the patient was given 0.01 ml/kg of solution (i.e. 100 i.u./kg of heparin in the treated group) in the same fashion as in the first trial. Treatment was commenced as soon as possible after arrival at the hospital and was continued at 8-hourly intervals before and after the treatment of the fracture for a total period of 2 weeks. No patient was excluded after randomization.

The details of the patients are shown in Table III. The operations were performed using nitrous oxide-oxygen muscle-relaxant general anaesthesia and the operating table was horizontal.

Diagnosis of DVT: All patients were given 100 µCi of ¹²⁵I-labelled fibrinogen within 12 hours of admission and leg scanning was commenced on the first day after admission. No patient had a positive scan before operation. Scanning was continued for up to 3 weeks, one (or in some cases two) further injection of 100 µCi ¹²⁵I-labelled fibrinogen being given when the precordial count fell to an unacceptable level.

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Table I: PATIENT DETAILS AND OPERATIONS PERFORMED IN THE FIRST TRIAL

| | Heparin | Placebo |
|--|-----------------|-----------------|
| <i>Patients</i> | 122 (8) | 120 (20) |
| Age (yr) (mean \pm s.e.) | 49.0 \pm 1.3 | 48.5 \pm 1.3 |
| Preoperative hospital stay (d) (mean \pm s.e.) | 4.8 \pm 0.8 | 4.4 \pm 0.5 |
| Male | 48 (2) | 45 (10) |
| Female | 74 (6) | 75 (10) |
| Previous venous thrombo-embolism | 6 (0) | 14 (2) |
| Varicose veins | 16 (2) | 21 (6) |
| Malignancy | 18 (3) | 10 (4) |
| <i>Operations</i> | | |
| Duration (min) (mean \pm s.e.) | 128.4 \pm 4.2 | 133.1 \pm 5.3 |
| Biliary | 77 (5) | 87 (14) |
| Gastric | 29 (1) | 21 (5) |
| Laparotomy | 11 (1) | 6 (1) |
| Splenectomy | 4 (1) | 3 (0) |
| Pancreatic | 1 (0) | 3 (0) |

Figures in parentheses are the number of patients developing postoperative DVT.

Table II: PATIENTS EXCLUDED FROM THE FIRST TRIAL AFTER RANDOMIZATION

| | |
|-----------------------------|-----------|
| Operation cancelled | 2 |
| Preoperative DVT | 2 |
| Thoraco-abdominal procedure | 2 |
| Reoperation | 2 |
| Omission of an injection | 3 |
| Failure of isotope scanner | 9 |
| Total | 20 |

Table III: PATIENT DETAILS AND OPERATIONS PERFORMED IN THE SECOND TRIAL

| | Heparin | Placebo |
|----------------------------------|----------------|----------------|
| <i>Patients</i> | 25 (0) | 25 (12) |
| Age (yr) (mean \pm s.e.) | 74.5 \pm 1.5 | 76.7 \pm 1.4 |
| Male | 5 | 7 (3) |
| Female | 20 | 18 (9) |
| Fractured right femur | 14 | 11 (7) |
| Fractured left femur | 11 | 14 (5) |
| Obesity | 4 | 4 (2) |
| Malignancy | 3 | 7 (2) |
| Varicose veins | 11 | 12 (9) |
| Previous venous thrombo-embolism | 5 | 1 (1) |
| <i>Operations</i> | | |
| Nil | 2 | 0 |
| Thornton pin and plate | 10 | 14 (6) |
| Jewett's pin and plate | 4 | 6 (3) |
| Austin Moore prosthesis | 9 | 5 (3) |

Figures in parentheses are the number of patients developing postoperative DVT.

Table IV: COMPARISON OF INCIDENCE OF DVT IN THE HOT AND COLD PERIODS OF THE YEAR IN THE FIRST TRIAL

| | Nov.-April (hot) | | May-Oct. (cold) | |
|---------|------------------|---------------------|-----------------|-----------------------|
| | No. of patients | No. with DVT | No. of patients | No. with DVT* |
| Placebo | 49 | 3 (6%) [†] | 71 | 17 (24%) [†] |
| Heparin | 54 | 4 (7%) | 68 | 4 (6%) |

* Heparin v. placebo: χ^2 with Yates' correction = 7.48, $P < 0.01$.

[†] Nov.-April v. May-Oct. χ^2 with Yates' correction = 5.41, $P < 0.05$.

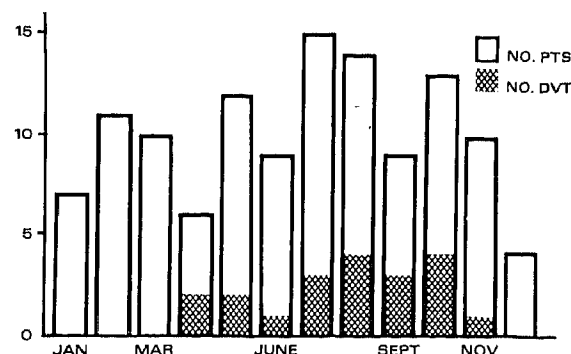


Fig. 1. Monthly incidence of DVT in the 120 control patients in the first trial.

All patients who developed a positive scan as defined above had ascending functional phlebography performed as described by Nicolaides et al. (1971). The scan result was confirmed in every instance.

Withdrawal of patients

In each trial any patient who developed a positive scan was withdrawn from the trial and then managed by the appropriate surgeon. In addition, provision was made in each trial for a patient to be withdrawn if excessive bleeding occurred, although this did not prove necessary.

Results

First trial

Two hundred and sixty-two patients began the trial, of whom 20 were excluded for the reasons shown in Table II. Thus, 242 patients completed the trial which lasted from July 1971 to September 1973. Eight patients of 122 (7 per cent) in the heparin-treated group and 20 of 120 (17 per cent) in the placebo group developed a postoperative deep vein thrombosis. This difference is significant (χ^2 with Yates' correction = 5.10, $P < 0.05$).

In the control group there were two long runs of consecutive patients in whom no DVT occurred (one run of 23 patients, the other of 27). This distribution is highly significantly non-random; the expected number of runs of 23 or more patients without DVT ($1 \pm$ standard deviation) is 0.30 ± 0.47 (Documenta Geigy, 1962). The observed number of runs in our trial was 2, this being significantly greater than 1 ($P = 0.0002$). Thus the incidence of DVT was not constant throughout the period of the trial. The intervals without occurrence of DVT extended from October 1971 to April 1972 (27 patients) and from November 1972 until April 1973 (23 patients). These two periods roughly cover the duration of Sydney's hot weather. The total number of control patients admitted to the trial each month and the monthly incidence of DVT are shown in Fig. 1. If the year is divided into a hotter 6-month period (November to April) and a colder 6-month period (May to October), the incidence of DVT in the colder 6 months (24 per cent) was significantly higher than that during the hotter 6 months (6 per cent) (Table IV).

This difference in incidence was more pronounced in patients over 40 years of age; 2 of 34 patients (6 per cent) developed postoperative DVT during the hot period as compared with 14 of 46 patients (30 per cent) in the cold period (χ^2 with Yates' correction =

5.91, $P < 0.02$). It was during the colder period of the year that low dose heparin was effective in preventing postoperative DVT (Table IV).

Unfortunately the daily temperatures for the hospital wards were not recorded. The maximum and minimum temperatures for each day of the trial were therefore obtained from the Sydney Bureau of Meteorology. The rise and fall of temperature, and the average temperature, for the 2 days before the day of operation and for the 2 days after operation were calculated for each patient in the control group. The patients were then ranked in order for each of these values, and the ranks divided into 12 groups of 10 patients. Using Kendall's coefficient of rank correlation, the correlation between the number of patients per group developing DVT and the rise or fall in temperature and the average temperature was determined (Tables V, VI). There were significant negative correlations between the incidence of DVT and the average temperature for each half day from the morning of the preoperative day up to the second postoperative day. There were also significant positive correlations between the incidence of DVT and the fall in temperature from the day before operation to the morning of the operation day, and also the fall in temperature from the operation day to the next morning.

Second trial

The results of the second trial are summarized in Table VII. Twelve of the 25 patients in the control group developed DVT during the first 2 weeks postoperatively, whereas there were no cases of DVT in the 25 treated patients (χ^2 with Yates' correction = 18.53, $P < 0.0005$). However, 4 patients developed DVT within 8 days of stopping the heparin, and 2 of these patients subsequently had pulmonary emboli. These 4 episodes all occurred during the cold period of the year.

Table VIII shows the incidence of DVT in the control patients during the hot and cold 6 months of the year. The incidence was found to be significantly higher in the cold 6 months (χ^2 with Yates' correction = 4.87, $P < 0.05$).

Bleeding and wound complications

The detailed results of the two trials will be presented elsewhere, but in neither trial was there any significant difference between treated and control groups with respect to bleeding during or after surgery, wound haematoma or wound infection.

Discussion

The results of these clinical trials have demonstrated that the incidence of postoperative DVT is not constant in these two hospitals and that many more cases of DVT occurred in the cold 6 months of the year than in the hot period. In the first trial, there were significant correlations between the incidence of DVT and the average temperature and the diurnal variation in temperature during the perioperative period. Heparin was found to be effective in significantly reducing the incidence of postoperative DVT, and had its greatest effect during the cold 6 months of the year.

The suggestion that the incidence of DVT and pulmonary embolism may be influenced by climatic or seasonal factors is not new, but this is the first

Table V: CORRELATIONS BETWEEN THE AVERAGE TEMPERATURE AND THE INCIDENCE OF DVT IN THE CONTROL PATIENTS IN THE FIRST TRIAL

| Average temperature | Kendall's correlation coefficient | P |
|----------------------------|-----------------------------------|--------|
| Min. day -2 to max. day -2 | -0.30 | 0.17 |
| Max. day -2 to min. day -1 | -0.39 | 0.08 |
| Min. day -1 to max. day -1 | -0.54 | 0.01* |
| Max. day -1 to min. day 0 | -0.52 | 0.02* |
| Min. day 0 to max. day 0 | -0.58 | 0.008* |
| Max. day 0 to min. day +1 | -0.54 | 0.01* |
| Min. day +1 to max. day +1 | -0.57 | 0.01* |
| Max. day +1 to min. day +2 | -0.52 | 0.02* |
| Min. day +2 to max. day +2 | -0.53 | 0.02* |

* Significant correlation.
- or +, Days before or after operation.

Table VI: CORRELATIONS BETWEEN THE RISE AND FALL IN TEMPERATURE AND THE INCIDENCE OF DVT IN CONTROL PATIENTS IN THE FIRST TRIAL

| Temperature | Kendall's correlation coefficient | P |
|---------------------------------|-----------------------------------|--------|
| Rise min. day -2 to max. day -2 | 0.25 | 0.26 |
| Fall max. day -2 to min. day -1 | 0.10 | 0.65 |
| Rise min. day -1 to max. day -1 | 0.32 | 0.15 |
| Fall max. day -1 to min. day 0 | 0.61 | 0.005* |
| Rise min. day 0 to max. day 0 | 0.39 | 0.08 |
| Fall max. day 0 to min. day +1 | 0.48 | 0.03* |
| Rise min. day +1 to max. day +1 | 0.22 | 0.33 |
| Fall max. day +1 to min. day +2 | 0.03 | 0.88 |
| Rise min. day +2 to max. day +2 | 0.42 | 0.06 |

* Significant correlation.
- or +, Days before or after operation.

Table VII: RESULTS IN THE SECOND TRIAL

| | Heparin | Placebo |
|-----------------|---------|---------|
| No. of patients | 25 | 25 |
| No. with DVT | 0 | 12 |

χ^2 with Yates' correction = 18.53 ($P < 0.0005$).

Table VIII: COMPARISON OF INCIDENCE OF DVT IN THE HOT AND COLD PERIODS OF THE YEAR IN THE SECOND TRIAL (CONTROL PATIENTS)

| | Nov.-April (hot) | May-Oct. (cold) |
|-----------------|------------------|-----------------|
| No. of patients | 15 | 10 |
| No. with DVT | 4 | 8 |

χ^2 with Yates' correction = 4.87 ($P < 0.05$).

demonstration of such a relationship using an accurate method of diagnosis of DVT. There are reports in the European literature suggesting an association between the occurrence of pulmonary embolism and the preceding passage of a meteorological front or period of stormy weather (Raettig and Nehls, 1940; Merz, 1948). The increased incidence was attributed to the change in either temperature or barometric pressure. The same suggestion has been made by other authors, particularly DeTakats et al. (1940), who reported that pulmonary embolism was more common in the spring and autumn, and Newton (1951), who found that clinically diagnosed postoperative DVT was more common in the same periods. Allen et al. (1945) reported that DVT and pulmonary embolism were commoner in the winter and Feinleib (1972), examining recent vital statistics for the United States, showed a definite seasonal fluctuation in deaths

from diseases of veins, with the highest incidence during winter. Presumably, the vast majority of these deaths was due to pulmonary embolism. The only conflicting report we have found is that of Smyrnis and Kolios (1973) who suggested that DVT was common in the summer. Thus the weight of previous evidence supports the findings of this study.

Clearly, there are many factors which may have contributed to this seasonal variation. The most obvious are differences in the physical environment of our wards, or operating theatres, in winter as compared with summer. Our wards are heated by hot water radiators in winter and are not air-conditioned in summer. Thus, our patients are exposed to seasonal variations in temperature and barometric pressure. Tromp (1963, 1974) has reviewed the variety of effects such seasonal variations may have on basic physiological mechanisms. These effects are many, and include alterations in blood volume, plasma fibrinogen levels, clotting times and serum lipids—all of which might influence the incidence of DVT.

There is a very marked difference in the incidence of postoperative DVT reported from various centres around the world. The incidence varies from 30 per cent in patients over 40 in Europe (Negus et al., 1968; Kakkar et al., 1972), to 12 per cent in Khartoum (Hassan et al., 1973), 10 per cent in Malaysia (Cunningham and Yong, 1974) and 2.4 per cent in Thailand (Chumnijarakij and Poshyachinda, 1975). These differences may be partly explained by climatic factors, as the present study suggests, but clearly many other elements, e.g. diet and race, may be important. There is some evidence that there are differences in the incidence of postoperative DVT within Australia. In this study, carried out in the temperate climate of Sydney, the incidence in patients over 40 was 20 per cent; however, the incidence in subtropical Brisbane is approximately 12 per cent and that in Melbourne (which is much further south than Sydney) is at least 30 per cent (Williams et al., 1973). There is also evidence that the mortality rate from pulmonary embolism in Australia reflects the same pattern, i.e. lowest in Queensland and highest in Victoria, with the rate in New South Wales intermediate between the two (Williams et al., 1973).

Investigation of these differences may provide valuable information concerning the aetiology of venous thrombosis. It will also be important to determine whether similar results are obtained in other countries and other climates. In the present study, heparin was effective as a prophylactic agent only in winter; if this is true in other countries, then the implications for heparin prophylaxis are obvious in terms of cost and effectiveness. Finally, an important immediate application of the results is in the design of future trials and in the interpretation of the results of past trials. Any protocol must take into account the possibility of a seasonal variation in the incidence of DVT during the period of the trial.

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