PAPERS AND ORIGINALS

Effect of intravenous dextran 70 and pneumatic leg compression on incidence of postoperative pulmonary embolism

N L BROWSE, G CLEMENSON, N T BATEMAN, J I GAUNT, D N CROFT

British Medical Journal, 1976, **2**, 1281-1284

Summary

The incidence of pulmonary embolism and deep vein thrombosis was measured in 50 matched pairs of patients undergoing common surgical procedures with preoperative and postoperative ventilation-perfusion lung scans and the fibrinogen uptake test. One patient in each pair was treated with intravenous dextran 70 and pneumatic leggings.

The incidence of pulmonary embolism among the treated patients was significantly reduced from 24% to 8%, but the incidence of deep vein thrombosis was not significantly reduced (34% to 24%).

Introduction

The principal objects of current research into venous thromboembolism are preventing death from pulmonary embolism and abolishing deep vein thrombosis and its late sequelae.

The advent of the fibrinogen uptake test provided a test which gives an adequate measure of the incidence of deep vein thrombosis in the calf during life. Although it is reasonable to assume that preventing deep vein thrombosis will prevent pulmonary embolism one cannot assume the converse: that a technique that fails to prevent deep vein thrombosis will fail to prevent embolism. Consequently the definitive assessment of any form of prophylaxis must measure the incidence of pulmonary embolism. This can be done by assessing the incidence of fatal embolism or the incidence of all postoperative embolism. Neither approach is easy. Fatal embolism is rare (0·2-1·0% of cases) so many patients must be studied and the cause of every death confirmed by necropsy, and embolism during life is very difficult to diagnose because it is either silent or the physical signs it produces are similar to those of other common conditions.

When we were planning this trial in 1971 we knew that two clinical trials based on an assessment of the incidence of fatal embolism were already in their preliminary stages so we decided to try and assess the incidence of embolism during life and its relation to the presence of deep vein thrombosis in the calf detected with the fibrinogen uptake test.

Departments of Surgery and Nuclear Medicine, St Thomas's Hospital, London SE1 7EH

N L BROWSE, MD, FRCS, professor of vascular surgery
G CLEMENSON, research associate
N T BATEMAN, MRCP, lecturer in medicine
J I GAUNT, BSC, senior physicist
D N CROFT, MB, FRCP, consultant physician

Patients and methods

All the patients studied were undergoing general surgical procedures. Those undergoing vascular operations or any operation directly affecting the legs or the pelvic veins were excluded. The first patients admitted to the trial were allocated to the test or control groups by their central bureau number. Those with odd numbers entered the test group, those with even numbers the control group.

A card was then completed, recording the patient's age, sex, disease, and any previous thromboembolism and, after operation, the anaesthetic, the type of operation, and the blood loss. Once 20 patients had been randomly allocated to the test or control groups, the cards of all new patients were examined to see if their preoperative data would match that of any patient already studied. If they did they were put in the opposite group. If they did not they were randomly allotted to the test or control groups as already described. By this means two groups of patients were obtained who were exactly matched for the following factors: (*a*) sex; (*b*) age, within the same decade; (*c*) disease, subdivided into malignant or non-malignant, as well as actual disease—for example, cholelithiasis, duodenal ulcer, carcinoma of the stomach, diverticulitis, etc; (*d*) previous thromboembolism, judged by a definite clinical history of a deep vein thrombosis or pulmonary embolism; (*e*) anaesthetic, including the drugs used for premedication, induction, and analgesia, gases, and spontaneous or positive pressure ventilation; (*f*) type of operation—for example, cholecystectomy, simple mastectomy; (*g*) length of operation, to

within half an hour; (*h*) blood loss and severe hypotension during or after operation.

Some of those chosen to match another patient on the basis of the factors known preoperatively ultimately failed to match because a different operation was performed. These patients were kept in the trial and another patient sought to match both them and the patient with whom they had provisionally been paired. Some patients were never matched and had to be discarded from the trial.

Diagnosis of peripheral deep vein thrombosis—Deep vein thrombosis in the lower thigh and calf was detected with the fibrinogen uptake test as described by Negus *et al.*[1] A difference of 15 between adjacent points on the same leg or similar points on both legs persisting for more than 24 hours was taken to indicate a thrombosis. The legs were examined one, three, five, and seven days after operation, or daily if they became positive.

Diagnosis of pulmonary embolism—Clinical examination, chest *x*-ray examination, and ventilation-perfusion lung scanning, as described by Williams *et al*,[2] were performed one or two days before and seven days after operation. Embolism was diagnosed if a new defect appeared on the postoperative perfusion lung scan in the presence of a normal ventilation scan (mismatch) and was associated with a normal radiograph of that area. These criteria have been shown to correlate well with other evidence of embolism.[3-5] Changes in perfusion matched with changes in ventilation, *x*-ray changes, or clinical signs such as pyrexia, purulent sputum, rales, and dullness to percussion were excluded because we could not say whether these changes were due to infection or embolism. We may therefore have underestimated the incidence of embolism but, on the other hand, there was little doubt about the diagnosis in those cases that fulfilled our criteria.

Patient consent—The object of the investigations was fully explained to the patients before we obtained their written consent to participation in the trial.

Prophylaxis—The main object of the chosen prophylactic regimen was to give the best form of prophylaxis with the minimum of extra work. The control subjects were given no specific prophylaxis, while the test subjects were treated with pneumatic leggings and intravenous dextran 70. Pneumatic leggings (Flowtronaire Ltd), which compress the legs alternately to a pressure of 40 mm Hg for two minutes and then relax for two minutes, were applied when the patient was given the premedication (one hour before operation) and kept on and working until the patient was awake and asked for them to be removed. Dextran 70 500 ml was given intravenously from near the end of the operation (during wound closure or immediately afterwards). If the patient did not require an intravenous infusion for his routine care no more dextran was given. If the infusion was required for routine care another 500 ml was given during the 24 hours after the end of the operation and 500 ml in every subsequent 24 hours while the intravenous infusion was being used. This scheme was designed to avoid the use of an intravenous infusion just for prophylaxis (except for the first unit, begun during operation) and so prevent additional work for the house staff.

Assessment of results—The fibrinogen uptake tests were performed by a technician. The use of a timer and scaler rather than a ratemeter made the observation of the results an objective exercise not subject to observer bias. The results were recorded and interpreted by another observer who did not know which treatment the patient had received. The *x*-ray films and lung scans were made by the departments of radiology and nuclear medicine respectively. They were reported on by the staff in these departments, who were ignorant of the treatment, and by a second observer, who was also unaware of the method of treatment. Whenever the assessment of both observers agreed the patient was counted as having a definite embolus. Thus peripheral thrombosis and embolism were diagnosed "blind."

Results

One hundred patients, 50 pairs, were fully studied. The problems of matching the patients' anaesthetics and operations and obtaining all the requisite investigations were considerable, and the study took four years to complete.

Twenty-four pairs of patients were men and 26 were women. The mean age of all patients was 59 years. Two pairs had a history of previous thromboembolism. Fourteen pairs had malignant disease. In almost every pair the basic anaesthetics were thiopentone, suxamethonium, nitrous oxide, oxygen, and pethidine, with positive pressure ventilation.

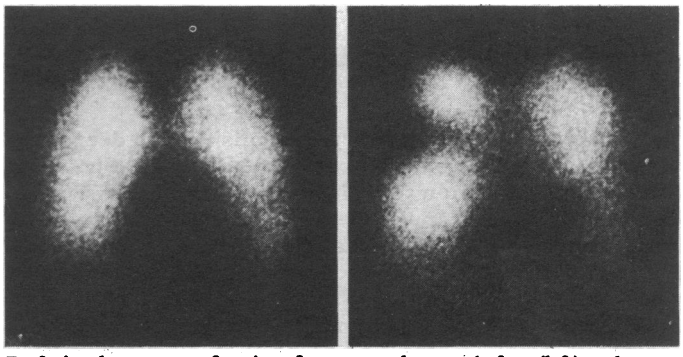
The operations performed were 20 pairs of gastrointestinal procedures (gastrectomy, vagotomy, etc), 12 pairs of cholecystectomies, seven pairs of sigmoid or right hemicolectomies, and 11 pairs of miscellaneous procedures.

No patient had postoperative hypotension (blood pressure below 100 mm Hg), and no patients received more than 2 units of blood.

Preoperative scans—Twenty patients (20%) had an abnormality on their preoperative ventilation-perfusion scan. In 10 the defect was present in both types of scan, nine had defects of perfusion alone, and one had a defect of ventilation alone.

Prophylaxis—All the patients in the test group wore their pneumatic stockings from premedication until waking from the anaesthetic. About one-third wore them for 24 hours but most asked for them to be removed once they were fully conscious, one to three hours after the end of the operation. Twenty patients received only one unit (500 ml) of dextran 70, the intravenous infusion not being required for routine care. Nineteen received 1000 ml dextran 70, their intravenous infusion being taken down 24 hours after operation, and 11 received 1500 ml dextran 70, as their intravenous infusion was required for two days.

Incidence of pulmonary embolism—Twelve patients in the control group developed a perfusion defect on their postoperative lung scan with a normal chest radiograph and normal ventilation scan. Four patients in the test group showed scanning evidence of embolism. Only four of these 16 patients had any clinical signs suggestive embolism. The difference between the two groups, 24% and 8%, was statistically significant ($P=0{\cdot}02$, using the Fisher exact test and $0{\cdot}025>P>0{\cdot}0125$ using McNemor's test for matched pairs). Many of the emboli that were clinically silent but detected by the lung scan were multiple and some were quite extensive (see figure). There were five emboli in the 14 control patients with malignant disease and two emboli in the 14 treated patients with malignant disease.



Perfusion lung scans of patient from control group before (left) and seven days after (right) operation. Multiple defects have appeared. Ventilation scan and chest radiograph were normal. Fibrinogen uptake test result was positive but the patient had no physical signs attributable to these emboli.

Incidence of deep vein thrombosis—Seventeen patients in the control group and 12 in the test group developed a positive fibrinogen uptake response in the first seven days after the operation. This reduction in the incidence of thrombosis, 34% to 24%, was much less than the two-thirds reduction in pulmonary emboli and was not statistically significant ($0{\cdot}15<P>0{\cdot}10$). In one patient the readings of the leg counts were equivocal: he had a difference of 20 on only one occasion, but he developed a definite embolism. In another patient the fibrinogen uptake test gave a negative result, but at 10 days he developed the physical signs of deep vein thrombosis, and a phlebogram was positive. Both of these patients were in the control group, and when they were counted as having definite deep vein thrombosis the reduction of thrombosis in the test group (38% down to 24%) was on the borderline of statistical significance ($P=0{\cdot}056$—Fisher exact test). All thromboses in both groups began below the knee. None extended above the knee, and there was no clinical evidence in any patient of iliofemoral thrombosis. There were seven patients with thrombosis among the 14 controls with malignant disease and five among the 14 who were treated.

Incidence of "matched" scan defects—Twelve patients developed matched changes in their ventilation-perfusion scans and chest radiographs after operation. Another four had matched perfusion scan and *x*-ray changes without any change in ventilation. All 16 patients

Relation between fibrinogen uptake test result and ventilation/perfusion defects after operation

	Number positive on fibrinogen uptake test	Number negative on fibrinogen uptake test
Perfusion, ventilation, and x-ray defect	3	9
Perfusion and x-ray defect	0	4
Perfusion defect only	13	3
No change	16	68

had a cough, sputum, mild pyrexia, and clinical signs of basal pneumonia, and all of the scan abnormalities were in the basal zones. Table I shows that the incidence of DVT in these patients was within the normal range. The incidence of thrombosis in patients with perfusion defects alone was much higher (see table).

Relation between positive fibrinogen uptake and pulmonary embolism—Thirteen of the 16 patients with a definite embolism were positive on the fibrinogen uptake test, and three were negative. Of the 84 patients without emboli 16 had a positive uptake and 68 were negative (see table). This relation between the presence of thrombus in the lower leg detected by the fibrinogen uptake test and the presence of a pulmonary embolus detected by ventilation-perfusion scanning was highly significant ($P < 0.0005$; χ^2 test). One of the three patients with embolism and no deep vein thrombosis had an equivocal fibrinogen uptake test result (a difference of 20 only once) and so was counted as negative. Another developed a clinically obvious thrombosis 10 days after operation. When these two were counted as having thromboses then the relation between lower leg thrombosis and embolism was still more significant. Nevertheless, this relation should not be interpreted as implying that the emboli came from the calf.

Side effects—No side effects from the pneumatic leggings or the dextran 70 were observed in any patients.

Discussion

This study was set up with four objectives: (*a*) to assess the incidence of postoperative embolism detectable by lung perfusion scanning; (*b*) to assess the relation between calf thrombosis and embolism; (*c*) to test a simple combined method of prophylaxis; and (*d*) to test the hypothesis that a reduction in the incidence of thrombi diagnosed by the fibrinogen uptake test is associated with a reduction in the incidence of pulmonary embolism.

INCIDENCE OF EMBOLISM ON LUNG PERFUSION SCANNING

The incidence of deep vein thrombosis in the controls was 34%, slightly higher than that recorded in other series, and the incidence of embolism was 24%—that is, two-thirds of the patients with small calf thrombi detected by the fibrinogen uptake test had pulmonary emboli large enough to be visible on a lung scan. These facts can be expressed in another way: one-third of the patients who survived surgery had deep vein thrombosis and a quarter had pulmonary emboli, a figure in keeping with the much higher incidence of deep vein thrombosis and embolism found in patients who reach the necropsy room.[6 7]

In view of the rarity of long-term pulmonary perfusion problems after surgical operations these emboli cannot seriously impair pulmonary function and are probably absorbed[8]; nevertheless, they do occur.

Twenty per cent of patients had a perfusion defect on their preoperation perfusion scan. This finding is of considerable importance because it shows that a preoperation control study is essential for this type of research. The results of any study which assesses the incidence of postoperative embolism from a single postoperative perfusion scan are meaningless.

RELATION BETWEEN CALF THROMBOSIS AND EMBOLISM

The relation between the presence of a calf thrombus and the appearance of a pulmonary embolus is clearly established. The present results support our previous ones.[9] The normal incidence of thrombosis in the patients with matched defects strongly supports our contention that matched defects are due to consolidation and infection, not embolism.

PROPHYLAXIS

The method of prophylaxis, which was designed to add little extra work to busy nursing and house staff, was effective. The dextran 70 was not begun at the beginning of the operation to avoid any increased bleeding. Recently published data[10] have shown, however, that dextran 70 does not cause extra intraoperative bleeding so it would be safe to begin the dextran infusion after the induction of anaesthesia and perhaps expect a greater reduction in the incidence of embolism.

There were too few patients with malignant disease for detailed statistical analysis, but the trend in the incidence of embolism, 35% in the controls and 14% in the treated patients, suggests that the prophylaxis is effective in the presence of malignant disease. Two of the four patients in the treated group who developed emboli had malignant disease and five of the 12 controls with malignant disease had emboli. Thus the proportion of patients with malignant disease among those who had emboli was the same in both groups.

The variability in the quantity of dextran 70 administered may reduce the scientific value of the study in terms of "dose-response" criteria, but it does reflect the severity of the operation, and the results suggest that such a method of administration is a reasonable compromise. Nevertheless, we cannot exclude the possibility that one unit of dextran given during the operation would have been just as effective as the variable, often larger, dose. The four patients in the test group who developed emboli were given 1, 1, 1·5, and 1·5 litres of dextran 70.

REDUCING THE INCIDENCE OF EMBOLISM AND THROMBI

The prophylaxis had a much smaller effect on deep vein thrombosis than on pulmonary embolism. Although a reduction of thrombi detected by the uptake test will be associated with a reduction of emboli because of the relation between them, it is apparently possible to change the incidence of embolism without changing the incidence of peripheral thrombosis. This conclusion agrees with the findings described by Kline *et al*[10] of the effect of dextran 70 on fatal embolism and deep vein thrombosis and emphasises the point that a method which fails to reduce thrombi detected by the uptake test should not be discarded because it might be effective for embolism. Some techniques, such as subcutaneous heparin, stop the peripheral thrombus forming, but others can apparently prevent it enlarging, fragmenting, and embolising.

The similarities between our results and those of Kline *et al*[10] in their study of dextran 70 alone, particularly the relatively small effect on leg thrombosis, suggest that the effective prophylactic agent as far as embolism was concerned was the dextran, not the pneumatic leggings, but this question requires further study.

This study does not answer the burning practical question: Which prophylaxis should I use? But it does show that the combination of a mechanical method and intravenous dextran 70 is effective and that trials of prophylaxis against embolism can be conducted using objective data obtained during life rather than at necropsy.

Ultimately the choice between subcutaneous heparin and dextran 70 will be resolved only when someone conducts a large clinical trial comparing not only the incidence of embolism during life and the incidence of fatal embolism, but most important of all, the overall mortality rates between the two groups.

We are extremely grateful to Mr H E Lockhart-Mummery and Mr B T Jackson for allowing us to include some of their patients in this trial and to the Trustees of St Thomas's Hospital Charitable Trust who have given us generous financial support.

References

1 Negus, D, *et al*, *British Journal of Surgery*, 1968, **55**, 835.
2 Williams, O, *et al*, *British Medical Journal*, 1974, **1**, 600.
3 McNeal, B J, Holman, B L, and Adelstein, S J, *Journal of the American Medical Association*, 1974, **227**, 753.
4 Croft, D N, *British Journal of Radiology*, 1976, **49**, 470.
5 Croft, D N, *European Journal of Nuclear Medicine*, 1976, **1**, 85.
6 Freiman, D G, Sugemoto, J, and Wessler, S, *New England Journal of Medicine*, 1965, **272**, 1278.
7 Coon, W W, and Coller, F A, *Surgery, Gynaecology and Obstetrics*, 1959, **109**, 487.
8 Allison, P R, Dunnill, M S, and Marshall, R, *Thorax*, 1960, **15**, 273.
9 Browse, N L, Clemenson, G, and Croft, D N, *British Medical Journal*, 1974, **1**, 603.
10 Kline, A, *et al*, *British Medical Journal*, 1975, **2**, 109.

Tobramycin, amikacin, sissomicin, and gentamicin resistant Gram-negative rods

F A DRASAR, W FARRELL, J MASKELL, J D WILLIAMS

British Medical Journal, 1976, **2**, 1284-1287

Summary

Sensitivities to gentamicin, sissomicin, tobramycin, and amikacin were compared in 196 gentamicin-resistant Gram-negative rods and in 212 similar organisms sensitive to gentamicin, mainly isolated from clinical specimens. Amikacin was the aminoglycoside most active against gentamicin-resistant organisms, Pseudomonas aeruginosa, Klebsiella spp, Escherichia coli, Proteus spp, Providencia spp, and Citrobacter spp being particularly susceptible. Most of the gentamicin-resistant organisms were isolated from the urine of patients undergoing surgery.

Gentamicin was the most active antibiotic against gentamicin-sensitive E coli, Proteus mirabilis, and Serratia spp. Pseudomonas aeruginosa and other Pseudomonas spp were most susceptible to tobramycin.

Introduction

Since 1964 gentamicin has proved valuable in treating severe infections caused by *Pseudomonas* spp, *Enterobacteria*, and related Gram-negative rods resistant to gentamicin.[1-4] In one hospital in Los Angeles 20% of clinical isolates of *Pseudomonas aeruginosa* and 50% of *Serratia marcescens* isolates were resistant to gentamicin[5] and 20% of Gram-negative rods isolated from sputum and blood in a group of hospitals in Japan were resistant to gentamicin.[6]

Gentamicin-resistant organisms have been isolated with increasing frequency at the London Hospital, and we have collected these strains to determine susceptibility to tobramycin, sissomicin, and amikacin. We also compared the activity of the four aminoglycosides against Gram-negative rods sensitive to gentamicin.

Department of Medical Microbiology, London Hospital Medical College, London E1
F A DRASAR, PHD, MRCPATH, senior lecturer in microbiology
W FARRELL, FIMLT, senior technician
J MASKELL, AIST, technician
J D WILLIAMS, MD, MRCPATH, professor of medical microbiology

Methods

One hundred and ninety-six strains of enterobacteria, *Ps aeruginosa* and other *Pseudomonas* spp, *Acinetobacter* spp, *Alcaligenes* spp, and *Flavobacterium* spp isolated from clinical specimens and which seemed to be resistant to gentamicin using a 10-μg disc were collected over 18 months. Four strains of gentamicin-resistant organisms from environmental sources were included. Another 212 strains of similar organisms sensitive to gentamicin by disc testing were collected over three months.

The minimum inhibitory concentrations (MIC) of gentamicin, sissomicin, tobramycin, and amikacin were measured by the agar dilution technique using doubling dilutions of the antibiotic in DST

TABLE I—*Numbers of different species of gentamicin-resistant Gram-negative rods*

	No of species		No of species
Providencia spp	35	Indole-positive *Proteus*	11
Ps aeruginosa	32	*Pseudomonas* spp	8
Acinetobacter spp	27	*Klebsiella* spp	8
Enterobacter spp	25	*E coli*	7
Alcaligenes spp	14	*Flavobacterium* spp	7
K aerogenes	13	Others	9

TABLE II—*Specimens containing Gram-negative rods resistant to gentamicin**

	No of specimens		No of specimens
Urine	119	Pleural fluid	5
Wound swabs	26	Dialysis fluid	4
Sputum	18	Environment	4
Ear swabs	13	CSF	1

*For 6 specimens the sources were unknown

TABLE III—*Numbers of gentamicin-resistant Gram-negative rods occurring in different sites in the London Hospital**

	No of isolates		No of isolates
Medical wards	34	Surgical wards:	110
Outpatient clinics:	25	Renal	30
ENT	8	Neurosurgery	26
Surgical	6	Intensive therapy	12
Dermatology	5		

*For 27 isolates the sources were unknown