PAPERS AND ORIGINALS

Dextran 70 in Prophylaxis of Thromboembolic Disease after Surgery: A Clinically Oriented Randomized Double-blind Trial

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Summary

A randomized double-blind trial of prophylaxis of thromboembolism in surgical patients judged by clinical morbidity has been completed. Altogether 831 patients over 40 years of age who underwent elective surgery of the stomach, biliary system, or colon received either dextran 70 or normal saline before the operation.

Thirteen of the 435 patients on saline and three of the 396 on dextran developed pulmonary embolism. Eight of these 16 patients died of pulmonary embolism—seven in the saline group and one in the dextran group. As detected either clinically or by ^{125}I-fibrinogen scanning the incidence of deep vein thrombosis was similar in the two groups. There was no increased incidence of excessive bleeding in patients on dextran though clinical impression suggested that some patients on dextran bled excessively.

This trial showed that dextran 70 administered by intravenous drip during operation is effective in preventing pulmonary embolism and, in particular, reducing mortality from this cause. It seems to be as effective as subcutaneous heparin but is easier to administer and places less of a burden on nursing services.

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Introduction

As surgical operations have steadily become safer over the past 30 years thromboembolism has emerged as one of the major residual causes of morbidity and mortality and one which has proved the most resistant to control measures. Because thromboembolism may be silent much research has been directed towards finding new diagnostic techniques for investigating the patency of the leg veins and the presence of pulmonary emboli. The ^{125}I-fibrinogen method[1] has emerged as the most convenient and accurate technique, but there has been a tendency to judge the effectiveness of prophylactic regimens by the reduction in calf thrombi diagnosed by this test, especially since the high incidence of subclinical thrombi diagnosed by this method (20-40%) facilitates the achievement of statistical significance with small groups of patients. In parallel with this clinical signs, claimed (and to some extent shown) to be unreliable, have been almost completely neglected and little heed paid to the morbidity attributable to deep vein thrombosis (D.V.T.).

The primary question to be answered, however, is whether or not a prophylactic regimen decreases clinical morbidity and mortality. As the late morbidity of subclinical D.V.T. has not been established by a prospective study of patients with and without ^{125}I-fibrinogen-diagnosed thrombi the value to the patient of preventing a subclinical thrombosis is questionable. It is more logical to determine whether or not the clinical course of the patient has been altered by prophylactic regimen—that is, whether the treated group has suffered less pain, pulmonary embolism, or mortality and whether the control group has had to stay longer in hospital for treatment of an excess of established thromboembolic episodes. The execution of such a trial raises its own problems since many patients will be required to provide significant results, and in multicentre trials involving busy district hospitals problems of patient observation and documentation arise because clinical commitments inevitably take precedence over research.

Two main groups of prophylactic measures have been advocated for deep vein thrombosis: mechanical measures altering blood flow to the legs during operation and drugs administered in an attempt to alter one or more stages of the clotting process. We chose dextran 70 in saline as the agent in this trial because of Bonnar and Walsh's[2] results in gynaeco-

logical patients and Harper *et al.*'s[3] convincing objective evidence and because the regimen causes no extra work for busy hospital staff and is well suited to double-blind controlled techniques.

Design of Trial

Organization.—Surgeons at six hospitals within 20 miles of Cardiff took part in the study. To ensure accurate observation and documentation five medically qualified clinical assistants were appointed solely to assess the patients every second day. They first attended a one-week "orientation" course to familiarize themselves with the principles of the trial, standardize the methods of eliciting clinical signs of D.V.T., and understand the protocol and the forms to be used. Subsequently they met regularly to maintain standardization and to discuss their problems, and the trial co-ordinator (A.L.K.) visited the eight participating hospitals frequently. A secretary was allocated to the trial to handle documents received from the clinical assistants.

Patients.—To enter the trial patients had to be over 40 years of age and undergoing elective laparotomy for conditions of the stomach (including oesophagus and duodenum), colorectum, or biliary tract (including pancreas). Patients in whom laparotomy showed a condition other than disease of these sites remained in the trial but were treated as a fourth diagnostic (miscellaneous) group.

Treatment.—Bottles of normal saline and dextran 70 in normal saline were prepared in identical containers which were in random order in cases. The anaesthetist started 500 ml of the fluid at induction, and the second 500 ml was given shortly after the patient left the theatre. The rate of flow was at the discretion of the anaesthetist. The anaesthetist recorded the bottle number, the anaesthetic used, the length of the operation, the measured blood loss, and the surgeon's opinion of the amount of oozing.

Follow-up.—Subsequent assessment of the patients was made by the clinical assistant, who advised the surgeon if he suspected D.V.T. Management of such cases was according to the surgeon's instructions. The clinical assistants recorded leg pain, ankle oedema, distended veins, and tenderness of the calf. These were assessed as (*a*) present but not clinically suggestive of D.V.T. or (*b*) clinically suggestive of D.V.T. (a "significant clinical sign"). Suspected D.V.T. was confirmed by phlebography.[4] Confirmatory tests for suspected pulmonary embolus included electrocardiography, chest *x*-ray examination, lung scan if available, and necropsy. In addition to the clinical assessment of D.V.T. 214 patients at the University Hospital of Wales were examined by ^{125} I-fibrinogen scanning[1] to facilitate comparison with other trials using this technique. Three months after discharge from hospital all patients were re-examined by the clinical assistants to exclude D.V.T. or pulmonary embolism occurring after discharge or check progress of existing thromboembolic disease.

Analysis.—All results were analysed on the English Electric 475 computer at the Cardiff Computer Centre. The code of the numbering of the bottles was broken after 223 cases to make a preliminary assessment, which suggested that a statistically significant result might be achieved by the admission of 800 cases. The trial was continued double-blind and ended with 831 cases entered.

Definition of Thromboembolic Disease.—A patient was considered to have thromboembolic disease if he had one or more of the following three conditions. *Pulmonary embolism* was diagnosed in any patient who had significant clinical signs of pulmonary embolism (chest pain, haemoptysis, dyspnoea, or collapse) whether confirmed by investigation or not, and in any patient dying suddenly whose death was considered by the pathologist at necropsy to be due solely to pulmonary embolism. *Clinical D.V.T.* was diagnosed in any patient who on two successive occasions had a "significant clinical sign" of D.V.T. (leg pain, ankle oedema, vein distension, or calf tenderness) and in whom a phlebogram was positive or not performed and also in any patient with any significant clinical signs on one occasion who died or developed a pulmonary embolism before a second examination. Any patient in whom the ^{125} I-fibrinogen test was positive and the phlebogram positive or not done was considered to have *isotopic D.V.T.*

Results

Of the 831 patients admitted to the trial 396 had been treated with dextran 70 solution and 435 with normal saline. The patients' age and sex, type of disease, length of the operation, and distribution between hospitals, were similar for both treatment groups.

Pulmonary Embolism.—There were 16 cases of pulmonary embolism detected during the trial, five at necropsy and 11 at assessment because they had significant clinical signs. Of these 11 the diagnosis was confirmed at necropsy in two and by investigations in eight. Thirteen (3·0%) of the patients had been treated by saline and three (0·8%) by dextran—a statistically significant difference ($P=0·02$). The relative risk for patients treated with dextran compared with those with saline was reduced to 0·25.

Clinical D.V.T.—There were 36 patients with clinically diagnosed D.V.T., of whom 20 (4·6%) had been treated with saline and 16 (4·0%) with dextran—a difference that was statistically insignificant. The relative risk was reduced to 0·8 for patients on dextran.

Isotopic D.V.T.—At the University Hospital of Wales 214 patients were examined routinely by the ^{125} I-fibrinogen test. Of the 57 in whom the test indicated a latent thrombosis 28 were examined by phlebography and in 23 the thrombi were confirmed. In the remaining 29 cases phlebography was not done and hence the isotopic diagnosis was not rejected. Fifty-two patients were therefore diagnosed as having isotopic D.V.T. Thirty-six cases would not have been detected by clinical methods and only 16 had associated clinical signs. Of the 52 patients 32 were on saline (26·4%) and 20 on dextran (21·3%). The difference was not statistically significant ($P>0·05$). The relative risk was 0·8 to the advantage of dextran cases.

Deaths.—Eighteen patients with thromboembolic disease died (see table); 14 (3·2%) had been treated with saline and four (1·0%) with dextran, which gave a relative risk of 0·3 for dextran cases. This was statistically significant ($P>0·05$). Eight patients with pulmonary embolism died and only one had been treated with dextran. In the seven patients treated with saline necropsies were performed with special reference to the trial but without knowledge of the treatment. In each case the pathologist considered pulmonary embolism to be the sole cause of death. These results are statistically significant whether one considers seven deaths on saline against one death on dextran ($P<0·05$) or seven confirmed cases on saline against none on dextran ($P<0·01$). These probabilities were calculated by Fisher's exact test. Case records of all other patients who died within three months of operation were reviewed but none was considered to have died of pulmonary embolism. There were 44 deaths without evidence of thromboembolism—23 dextran cases and 21 saline cases. Thirty-seven patients died of causes unrelated to cardiorespiratory disease (27 of terminal malignancy, three of cerebrovascular accidents, three of liver failure, and four of peritonitis). Seven patients (four saline, three dextran) died with chest complications other than thromboembolism (five patients with advanced malignancy also had bronchopneumonia and two patients with benign disease died of bronchopneumonia or myocardial infarction.

Increased Bleeding.—In 114 (13·7%) patients, of whom 58 (13·3%) were on saline and 56 (14·1%) were on dextran, increased oozing was recorded—a statistically and surgically insignificant difference. In spite of this objective assessment in four cases the clinicians requested that the code be broken at a time of excessive bleeding, and in all four cases the treatment was dextran. Two of these patients, whose wounds had been closed with suture tapes, had persistant oozing from the skin edges requiring replacement of the tapes by sutures several hours later. Subsequently, tapes were not used when skin oozing seemed to be excessive and the problem did not recur. The other two patients required transfusion for unexplained blood loss, but no further measures were required.

Other Characteristics.—A detailed analysis of the incidence of clinical D.V.T. by the characteristics of the patients suggested that older patients and patients with malignant disease or disease of the colorectum had a higher incidence of clinical D.V.T. The patients operated on at the University Hospital of Wales had a higher incidence

Number of cases of Thromboembolic Disease and Deaths within Three Months

	Saline		Dextran	
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths
Clinical D.V.T. alone	11	2	7	1
Pulmonary embolism alone	10	6	2	0
Isotopic D.V.T. alone	25	4	11	0
Clinical D.V.T. and pulmonary embolism	2	0	0	0
Clinical and isotopic D.V.T.	6	1	8	2
Clinical and isotopic D.V.T. and pulmonary embolism	1	1	1	1
Total with any clinical D.V.T.	20	4	16	4
Total with any pulmonary embolism	13	7	3	1
Total with any isotopic D.V.T.	32	6	20	3

of clinical D.V.T. than those in other hospitals, which seemed to be partially attributable to the higher proportion of patients with malignant disease treated in this hospital. There was no statistical significance in the distribution of these cases between the saline and dextran groups.

Discussion

This trial has shown that a worthwhile reduction in clinically significant pulmonary emboli, both fatal and non-fatal, can be achieved with a simple prophylactic regimen which carries no serious side effects. Six of the seven patients in the control group who died from pulmonary embolism had potentially curable lesions, so the use of dextran in the 435 control patients might have allowed six patients to live out a normal lifespan.

There have been few trials of dextran large enough to assess its effectiveness in preventing clinically significant pulmonary embolism. Jansen[5] reported similar results to ours though his groups were not large enough to yield statistical significance. And in a small group of very high risk patients undergoing radical surgery for pelvic cancer (45 treated with dextran, 45 controls) Bonnar *et al.*[6] reported a similar (though statistically insignificant) reduction in pulmonary embolism with five cases (two fatal) in the control group and one non-fatal case in the dextran group.

In contrast to its effectiveness in reducing pulmonary embolism the effect of dextran on venous thrombosis, both clinical and isotopic, in our series was minimal. Though there have been many other trials of this aspect of dextran treatment the results have varied widely so it is hard to relate our results to them. Similar discrepancies abound in published reports on the prophylaxis of thromboembolism and few trials have been large enough to give evidence of clinical benefit. Two other features of trials may also have an effect on their outcome: whether or not the trial is double-blind, and the degree of heterogeneity of the groups of patients. In our trial blind assessment was important in determining side effects of treatment, and like Bonnar and Walsh[2] who used the same regimen, we found no excess morbidity in the dextran group. Smith,[7] however, counselled against the use of dextran, believing that his high incidence of haematoma in an uncontrolled trial was due to the dextran administration.

OTHER PROPHYLACTIC MEASURES AGAINST THROMBOEMBOLISM

Phenindione prophylaxis reduces significantly pulmonary embolism in patients over the age of 55 suffering from fractured neck of femur[8]; pulmonary embolism was reduced from 18% to 4% and fatal emboli from 10% to 1·3%. Mechanical prophylactic measures such as calf compression and calf stimulation have been reported only in relation to calf thrombosis detected by ^{125}I-fibrinogen. Most reports on the use of subcutaneous heparin also relate to diagnosis with ^{125}I-fibrinogen, though two have shown a considerable reduction in pulmonary embolism. Sagar[9] has reported a significant reduction in fatal pulmonary emboli after the use of subcutaneous mucous heparin sodium in a dose of 5000 units 12 hourly for five days. A multicentre randomized (but not double-blind) study of 2055 patients which is still in progress has shown a decrease in pulmonary embolism in patients treated with subcutaneous heparin; only one patient so treated has died of pulmonary embolism compared with seven controls. Pulmonary embolism has also contributed to the deaths of two further patients in each group.[10]

Hence dextran 70 and subcutaneous heparin seem to have a comparable effect in prevention of pulmonary embolism. So many patients would be needed to show a significant difference between these two methods of treatment that such a trial would not be worthwhile, so the advantages of the administration of dextran over that of subcutaneous heparin (in relation to the burden on N.H.S. facilities) may prove to be decisive in the choice of a prophylactic agent.

DIAGNOSIS OF D.V.T. AND PROPHYLAXIS OF PULMONARY EMBOLISM

Our clinical diagnosis of D.V.T. was very accurate, being confirmed by phlebography in 18 out of 20 patients. A smaller correlation was obtained between clinical diagnosis and isotopic diagnosis. Fifty-seven (26·6%) out of 214 cases were positive by the ^{125}I-fibrinogen test. Phlebography showed five out of 28 (17·9%) to be false positives, and of the 57 cases suspected by the isotope method 40 (70·2%) were not suspected by clinical diagnosis. The two groups are not comparable, however, since the ^{125}I-fibrinogen method detects earlier lesions, and this is borne out by the fact that 77% of scan-positive, clinically negative patients were positive on phlebography. The high degree of accuracy (as determined by phlebography) of both clinical and isotopic diagnosis of D.V.T. justified our counting as positive those cases judged to have clinical signs but not examined by phlebography.

We must ask whether we should expect that diagnostic techniques which are more effective in detecting minor degrees of calf vein thrombosis should be valid in assessing prophylaxis against serious morbidity and mortality. It is clear from necropsy studies, venography, and the results of direct surgery that clinical morbidity is related to thrombosis in the ileofemoral segments and that calf vein thrombosis has little clinical significance except in its relation to major vein thrombosis.[11] Though the two types of thrombi may be related they may have different causes, in which case a specific prophylactic measure may well be more effective in preventing one type of thrombosis than another. Further support for this concept comes from a study of the prophylactic effect of subcutaneous heparin in relation to both subclinical thrombosis (as assessed by the ^{125}I-fibrinogen test) and subclinical pulmonary embolism (as detected by ^{99m}Tc-ferric hydroxide lung scanning).[12] Only six out of 35 patients with pulmonary emboli had coexisting leg thrombosis, showing the absence of correlation between pulmonary emboli and D.V.T. as detected by ^{125}I-scanning. The findings of this study agreed with those of Sevitt and Gallagher,[8] who found that a reduction of mortality and morbidity from pulmonary embolism in patients taking phenindione was not accompanied by a corresponding diminution of small calf vein thrombosis at necropsy.

Thus, while the ^{125}I-fibrinogen test has contributed much to an understanding of the frequency of subclinical calf thrombosis, this may be causing as much confusion as help in understanding serious clinical disease. Indeed, one must ask whether the use of the ^{125}I-fibrinogen test in the assessment of prophylactic measures related to pulmonary embolism should be abandoned. If it were, large clinical trials of well-defined homogeneous groups of operations would be necessary to provide comparison in terms of true clinical benefit of different agents such as heparin or dextran versus mechanical methods. Such studies would inevitably be tedious, time consuming, and, if adequately controlled and documented, very costly. Yet the cost would be no greater than that of many small trials or poorly controlled multicentre trials which give rise to inconclusive or misleading results.

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secretary, Mrs. Barbara Holland, whose efforts played a major part in bringing it to a satisfactory conclusion.

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Effects of Truncal, Selective, and Highly Selective Vagotomy on Glucose Tolerance and Insulin Secretion in Patients with Duodenal Ulcer

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Part I—Effect of Vagotomy on Response to Oral Glucose

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Summary

An oral glucose tolerance test was performed in patients who had undergone truncal vagotomy and pyloroplasty, bilateral selective vagotomy and pyloroplasty, or highly selective vagotomy without a drainage procedure at least six months earlier. The results were compared with those from patients with chronic duodenal ulcer before operation. In all three groups of patients after vagotomy more rapid rates of rise of blood glucose and higher peak concentrations were observed than in patients who were tested before operation. These differences were statistically significant only in patients who had undergone truncal or selective vagotomy with pyloroplasty and were probably due to more rapid rates of gastric emptying after these operations.

Plasma insulin concentrations were lower after truncal vagotomy than after selective or highly selective vagotomy, the difference between truncal vagotomy and highly selective vagotomy being statistically significant. Truncal vagotomy resulted in a diminished insulin response to oral glucose, which could have been due to vagal denervation of the pancreas or, more probably, impaired release of small-bowel hormones which normally augment the pancreatic insulin response.

Introduction

Patients with chronic duodenal ulceration exhibit abnormal glucose tolerance and insulin secretion, which might be due to abnormal secretion of one or more small-bowel hormones.[1]

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Vagotomy—whether truncal, selective, or highly selective—produces changes in the pattern of gastric emptying[2-4] and thus might alter the disposal of a glucose meal. Vagotomy might also interfere with the synthesis, release, or action of gastrointestinal hormones which modify the insulin response to ingested carbohydrate.[5 6] We therefore investigated the effect of vagotomy on carbohydrate metabolism. Three types of vagotomy were studied: truncal vagotomy and pyloroplasty, in which the stomach, small bowel and proximal large bowel, liver, biliary tract, and pancreas are vagally denervated; bilateral selective vagotomy and pyloroplasty, which denervates the entire stomach but preserves the parasympathetic innervation of the extragastric viscera via the hepatic and coeliac branches of the vagus; and highly selective vagotomy, which preserves the nerve supply to the gastric antrum as well and thus obviates the need for a drainage procedure.

Patients and Methods

Four groups of 15 patients were studied: patients with duodenal ulcer before operation, and patients who had undergone each of the three types of vagotomy at least six months earlier (table I). The group of patients suffering from chronic duodenal ulcer has been described.[1] The postoperative patients were all in good health, with no evidence of gastric retention, and eating a normal diet. All patients were within 10% of their ideal body weight, and none gave a history of diabetes. Each vagotomized patient had undergone an insulin test soon after operation which had shown that the vagotomy of the parietal cell mass was complete.[7] In each case the diagnosis of duodenal ulceration had been confirmed at the time of operation.

PROCEDURE

The glucose tolerance test was carried out after the patient had fasted overnight. The patient drank the test meal (350 ml of a 25% solution of glucose) while standing. After the first 10 minutes the patient sat in a chair until the end of the two-hour test. Venous blood samples were withdrawn through an indwelling heparinized cannula before the test and at 10, 20, 30, 45, 60, 90, and 120 minutes.

Blood glucose concentrations were measured on an autoanalyzer by Morley *et al.*'s method,[8] the coefficient of variation being 4·6% at a blood concentration of 5·83 mmol/l (105 mg/100 ml). Plasma immunoreactive insulin was measured in duplicate.[9] Radioactive iodinated insulin and Oxoid membrane filters were supplied by the Radiochemical Centre, Amersham. The pre-precipitated antibody and standard human insulin were supplied by Burroughs Wellcome.