PAPERS AND ORIGINALS

Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: interim report of prospective trial

Groote Schuur Hospital Thromboembolus Study Group

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Summary and conclusions

The efficacy of low-dose subcutaneous heparin (5000 IU eight-hourly) is being studied in a single-centre, prospective randomised trial of patients aged over 40 submitted to major elective intra-abdominal surgery. The trial end-points are the objectively defined incidence and extent of deep vein thrombosis (as seen on uptake of ^{125}I-labelled fibrinogen, Doppler ultrasonography, and bilateral ascending phlebography) and non-fatal pulmonary embolus (as measured by preoperative spirometry and preoperative and postoperative chest radiography and perfusion lung scanning performed on a routine, unselected basis). An interim analysis of the first 200 patients indicates that low-dose heparin significantly reduces the incidence of calf-vein thrombosis but does not reduce the incidence of proximal segment thrombosis or non-fatal pulmonary embolism.

Thus the routine use of low-dose heparin prophylaxis in all major surgical procedures in patients aged over 40 may not be advisable.

Groote Schuur Hospital, The University of Cape Town, and the Institute for Biostatistics of the Medical Research Council of South Africa

Members of the study group are:
E J IMMELMAN, FCS, FRCS, associate professor of surgery
P JEFFERY, FCS, FRCSED, lecturer in surgery
S R BENATAR, FFA, MRCP, senior lecturer in respiratory clinic
M S ELLIOT, FRCS, FRCSED, lecturer in surgery
J A SMITH, MMED(RAD D), MMED(NUC MED), senior lecturer in nuclear medicine
M R FUNSTON, DMRD, FRCR, senior lecturer in radiology
B J SHEPSTONE, DPHIL, DMRD, head of department of nuclear medicine
A D FERGUSON, MB, FRCP, head of respiratory clinic
P JACOBS, MD, PHD, professor of haematology
J P G PRETORIUS, MSC, senior chief research officer
J H LOUW, CHM, FRCS, professor of surgery

Introduction

In 1975 Kakkar *et al* published the now well-known findings of the international multicentre trial, which appeared to establish conclusively the effectiveness of low-dose heparin in preventing fatal postoperative pulmonary emboli.[1] Sherry outlined the numerous defects of this trial but concluded that it nevertheless provided, with a high degree of probability, the final link in establishing the validity of low-dose heparin prophylaxis.[2] Further doubts were cast on the results, however, by Gruber's report[3] of a high incidence of fatal pulmonary embolism (PE) in heparin-treated patients, in particular because his patients had been included in the multicentre study. Reanalysis of the multicentre data, excluding Gruber's cases, suggested that the initial conclusions were still valid.[4] The inconsistencies and possible sources of error in the multicentre trial highlighted by these reports, however, have led to considerable doubt about the true value of prophylactic low-dose heparin.

As it is unlikely that a more definitive multicentre trial, with fatal PE as the end-point, will be mounted, the alternative of a more careful investigation of the anatomic distribution of deep vein thrombosis (DVT) and the incidence of all pulmonary emboli in control and treated patients is needed to provide convincing evidence of the value or otherwise of any prophylactic method. With the intention of carrying out such a study, using carefully defined criteria for DVT and PE, we began a single-centre, prospective, randomised controlled trial in 1975. The trial is still in progress but, because of the current controversy over the effectiveness of low-dose heparin, we here report on the first 100 control and 100 heparin-treated patients.

Patients and methods

We included in the trial patients over the age of 40 undergoing major, elective intra-abdominal surgery. To ensure a homogeneous test population we studied only general surgical patients. Major surgery was defined as an intraperitoneal procedure lasting more than 30 minutes under general anaesthesia and requiring seven or more days in hospital postoperatively. Patients receiving oral anticoagulants or antiplatelet agents and those undergoing intra-abdominal vascular

surgery were excluded. We also excluded black African patients because they may possibly have a lower incidence of thromboembolic disease. The trial protocol was accepted by the Hospital and University Ethical Trials Committee and fully informed written consent obtained from each patient.

DESIGN OF STUDY

The trial was designed as having three concurrent stems. We predicted that if prophylaxis were capable of at least halving the generally assumed incidence of both DVT and non-fatal PE, then entering 200 patients into each stem would be enough to give the trial an 80% probability of detecting a significant difference at the 5% level. The first stem comprises control patients receiving no prophylaxis. Patients in the second stem receive prophylactic low-dose subcutaneous heparin. The first 100 patients received sodium heparin and the second 100 are receiving calcium heparin. In the third stem other forms of prophylaxis are being examined. As the third stem and the calcium heparin part of the second stem are still in progress only the first 100 patients who received heparin and their randomised, concurrent controls are reported on here. Randomisation, using a computer-generated table of random numbers, was performed by a non-member of the trial team. All patient information was entered on to data sheets for computer analysis. To avoid bias, once a patient had entered the study that patient was monitored to conclusion, irrespective of whether all screening procedures had been performed or a single dose, or more, of heparin omitted. Patients were, however, excluded from the trial if the operation was cancelled after randomisation, if preoperative DVT was detected on ^{125}I-labelled fibrinogen uptake scanning, if the operation lasted less than 30 minutes, if intraoperative death occurred, or if there was early voluntary withdrawal. All results were assessed blind by observers.

Diagnosis of DVT—DVT was diagnosed by a combination of screening procedures. These included the ^{125}I-fibrinogen test with uptakes measured preoperatively and daily thereafter, using the technique and criteria described elsewhere.[5] Every second day after operation the legs were examined clinically and by Doppler ultrasound using the methods and criteria of Evans and Cockett.[6] On the sixth postoperative day bilateral ascending phlebography was performed, using the method described by Rabinov and Paulin.[7]

Diagnosis of postoperative PE—On the day before surgery patients underwent four-view perfusion lung scanning (technetium-99m MAA Nuclear Chicago Pho-Gamma III Camera), posteroanterior and lateral chest radiography, and spirometry before and after receiving bronchodilators. On the seventh postoperative day the chest radiography and perfusion lung scans were repeated. The postoperative scan was read in conjunction with the postoperative chest radiograph to exclude visible densities as the cause of perfusion defects, and with the preoperative spirometric results to ascertain whether patchy perfusion defects could be attributed to obstructive lung disease. The preoperative chest radiograph and lung scan were studied simultaneously to exclude pre-existing defects. To lend objectivity to such an assessment a scoring system consisting of combinations of the above investigations was used. The degree of confidence with which new postoperative perfusion defects were regarded as representing PE was reflected in the score: 0/6 no evidence of PE; 1/6-3/6 PE possible but unlikely; 4/6-5/6 highly probable; and 6/6 definite. Only patients with well-defined defects on the postoperative scan and normal preoperative and postoperative radiographs, preoperative scans, and spirometry could score 6/6.

Adverse effects and deaths—No formal measure of operative blood loss was made. Instead, surgeons, who did not know the patients' treatment, were asked to comment on operative bleeding. When postoperative blood loss, via drains, wounds, or nasogastric tubes, was judged to be excessive this was recorded, as was the development of wound haematomata. When heparin was withdrawn because of bleeding, this was noted. Deaths were considered to be due to PE if a major clot that had formed before death was found in the pulmonary trunk or main pulmonary artery and no other cause of death was found at necropsy.

Prophylactic schedule—Patients randomised to heparin received sodium heparin (Novo) by subcutaneous injection, 5000 U two hours preoperatively and 5000 U eight-hourly postoperatively for six days or until fully ambulant. The injection was made by a standard technique via a 26-gauge needle into a skin fold on the anterior abdominal wall.

Statistical analysis—Fisher's exact probabilities were calculated for all two-by-two tables, and the maximum likelihood χ^2 was used for two-by-three tables.[8]

Results

Out of 205 available patients, six were excluded under the above criteria, leaving 99 controls and 100 patients receiving heparin. Table I shows the distribution of risk factors and operative procedures. Statistical analysis showed that the groups were well matched, with no significant difference in distribution. Table II shows the incidence of DVT. Whatever mode of assessment was used, the overall incidence of DVT was significantly reduced in the patients who received heparin compared with the controls. Fewer patients were available for phlebographic analysis because some were too ill for or refused phlebography and in some the radiographs were not of diagnostic quality.

TABLE I—*Details of patients accepted into trial*

	Controls	Patients receiving heparin
No acceptable for analysis	99	100
Men	52	53
Women	47	47
Mean (± SD) age (years)	60·9 ± 11·4	59·8 ± 11·3
Mean (± SD) height (cm)	165 ± 10·5	164 ± 10·9
Mean (± SD) weight (kg)	63·1 ± 12·5	62·1 ± 13·5
No with history of DVT or PE	4	5
No with varicose veins	19	17
Mean (± SD) No of days spent in hospital preoperatively	4·0 ± 3·9	4·6 ± 3·5
Operations:		
Gastric	41	40
Biliary or pancreatic	22	20
Colorectal	16	20
Miscellaneous	20	20
No with malignant disease	36	37

TABLE II—*Incidence of DVT as measured by leg-screening procedures*

	Controls	Patients receiving heparin
^{125}I-fibrinogen uptake		
No available for analysis	99	100
No (%) in whom DVT diagnosed	27 (27)	12 (12)
P	0·0074	
Phlebography		
No available for analysis	83	85
No (%) in whom DVT diagnosed	22 (27)	11 (13)
P	0·033	
^{125}I-fibrinogen uptake and phlebography combined		
No available for analysis	99	100
No (%) in whom DVT diagnosed	29 (29)	14 (14)
P	0·0099	

TABLE III— *Phlebographic distribution of thrombi. (Figures are numbers of patients)*

	Controls	Patients receiving heparin
No DVT	61	74
Unilateral DVT	10	6
Bilateral DVT	12	5
Overall χ^2	5·4	
P	0·066	
Anatomical site of DVT		
No DVT	61	74
Calf	18	6
Femoral/ileofemoral	4	5
Overall χ^2	8·3	
P	0·016	

Table III shows the anatomical distribution of DVT as determined phlebographically in the two groups. Among the patients developing DVT the proportions with bilateral clot were about equal (12/22 *v* 5/11). DVT restricted to the calf was present in 18 controls and six patients receiving heparin, whereas femoral or iliofemoral clots were present in an additional four patients (six legs) in the control group and five patients (five legs) in the heparin group. In two of the affected legs in the control group and two in the heparin group there was an isolated clot in the proximal segment, and these were all non-occlusive. Thus although the anatomic distribution of clots in

the patients receiving heparin was significantly different from that in the controls (P = 0·016), this was achieved entirely by reducing the incidence of calf-vein thrombosis. Importantly, of the nine patients with femoral or iliofemoral thrombosis on phlebography, three with isolated proximal clot had normal ^{125}I-fibrinogen uptakes, while in a fourth patient fibrinogen uptakes failed to delineate superficial femoral vein propagation. Of the 43 patients judged to have DVT by the leg-screening procedures, 39 had clinically silent thromboses. Doppler ultrasound proved uniformly negative in patients with calf-vein thrombosis but correctly identified six of the nine patients with proximal segment clots.

Table IV shows the PE data. Eighty-eight controls and 95 patients who received heparin had complete protocols to permit scoring.

TABLE IV—*Results of PE screening*

Group	No in group	Total No (%) scoring 1·6-6·6	No (%) with possible PE (1·6-3·6)	No (%) with probable PE (4/6-5/6)	No (%) with definite PE (6·6)
Control	88	20 (23)	14 (16)	1 (1)	5 (6)
Heparin	95	23 (24)	14 (15)	4 (4)	5 (5)

P > 0·05 at each severity level.

Twenty (23%) of the control patients and 23 (24%) of the heparin patients had new postoperative perfusion defects and scored 1/6, or more, for suspected PE. Among these patients the diagnosis was considered to be definite (6/6) in five controls and five patients receiving heparin. The only death due to acute PE confirmed at necropsy was in a patient who received heparin, who is included in table IV. Four cases of PE in the heparin group, but none in the control group, were symptomatic. There was no statistical difference in the PE figures (P < 0·05 at each severity level). Table V shows the strong positive correlation between the phlebographic presence or absence of DVT and PE scores.

TABLE V—*Correlation between phlebographic presence or absence of DVT and PE scoring*

	No	Total No (%) scoring 1/6-6/6	No (%) scoring 6/6
Patients with no DVT	135	25 (19)*	4 (3)†
Patients with DVT	33	17 (52)*	6 (18)†

*P = 0·00023.
†P = 0·00044.

Table VI shows the numbers of patients who experienced bleeding and who died. Postoperative oozing was judged to be excessive in four control patients and eight who received heparin (in five of whom prophylaxis was stopped by the clinician in charge). This decision may have been a somewhat subjective one, as by this stage the attendant medical staff were not blinded. In no case was postoperative bleeding massive or life threatening, and there was no significant difference between the two groups (P = 0·37). Hospital deaths are included in table VI and were not significantly different (P = 0·28). Consent for necropsy could be obtained in only six control and two heparin patients. One patient receiving heparin, who died on the 12th postoperative day, was shown to have bilateral proximal segment DVT and massive PE filling both main pulmonary arteries. In the six hospital deaths in which necropsy was not carried out the cause of death was clear-cut. Two patients died of terminal cancer while receiving heavy analgesia. The causes of death in the remaining four patients were myocardial infarction, massive rectal bleeding, acute Mendelsohn's syndrome, and klebsiella pneumonia and septicaemia. Two of these patients developed DVT ante mortem and scored 1/6 and 2/6 respectively for PE; they are included in the tables.

TABLE VI—*Numbers of patients with complications due to bleeding and number dying*

Group	No in group	Complications			Deaths
		Operative bleeding	Postoperative bleeding	Wound haematoma	
Control	99	4	4*	2	9†
Heparin	100	3	8*	2	5†

*P = 0·37.
†P = 0·28.

Twenty-two patients receiving heparin missed one or more prophylactic doses, including the five patients in whom it was discontinued for bleeding. One patient whose heparin was discontinued on the second day already had DVT on fibrinogen uptake. None of the remainder developed DVT. These patients continued to be screened until discharge and are included in the tables. Fibrinogen uptakes were measured in the legs preoperatively in 111 of the 205 patients; only one was shown to have developed a preoperative DVT and was excluded from the trial. An analysis of the incidence of DVT in the hot months of the year compared with the cold months disclosed no suggestion of a seasonal fluctuation in either the control patients or the total trial population.

Discussion

Our study to date has shown that, although low-dose heparin significantly reduces the incidence of calf-vein thrombosis, it does not reduce the incidence of proximal segment clots or non-fatal pulmonary embolus, nor does there appear to be a trend towards such a reduction. Most earlier trials of low-dose heparin have relied solely on ^{125}I-fibrinogen uptakes as a screening procedure,[9] and few have attempted to define the incidence of non-fatal PE.[10 11] If we had relied on fibrinogen uptakes we would have overlooked the presence of proximal segment thrombosis in four of the nine patients so affected. Our results further suggest that it may be erroneous to assume that reducing the overall incidence of DVT will proportionately reduce the incidence of PE.

We have based our assessment of postoperative PE on the presence of abnormal areas of perfusion in the postoperative lung scan and have attempted to increase the specificity of this assessment by excluding other causes of perfusion defects. Several theoretical objections may be made about our scoring system. Firstly, it might be argued that localised areas of reduced ventilation could be present postoperatively in patients with chronic obstructive airways disease mild enough to escape detection by simple spirometry, and that ventilation perfusion scanning should have been performed. Logistically, this was not possible in our institution. A study by Browse[12] using xenon ventilation and perfusion scans before and after operation suggested an 18% incidence of postoperative PE, a figure not too dissimilar from our 22% of patients scoring 1/6 or more for PE. More-careful four-view ventilation scans, using krypton, combined with four-view perfusion scans, suggest the very much lower incidence of 4% by the sixth postoperative day,[13] a figure that seems more realistic and is similar to our 5% of 6/6 scorers.

The second objection might be that our scoring system should have been validated against pulmonary angiography in a sample of our patients. While this criticism is basically sound, the ethics of doing pulmonary angiography for suspected minor and usually silent PE is open to question and is likely to be unacceptable to patients. In addition, conventional angiography would not be enough; selective angiography would be necessary to show what might be relatively small vessel occlusions. Previous studies of the effect of prophylaxis on PE have had criteria for diagnosing this far short of ours, and the stringent criteria for scoring 6/6 in our study ensure that PE was underdiagnosed rather than overdiagnosed. The remainder of the lower scores permit an assessment of the range of underdiagnosis.

We believe that a sweeping recommendation for the routine use of low-dose heparin prophylaxis in all major surgical procedures in patients aged over 40 years[14] may be premature on available evidence. The choice of appropriate end-points (proximal segment DVT and non-fatal PE) defined by currently available, objective screening procedures in patients postoperatively may, in the near future, provide the answer to the vexed question of "What is the best prophylactic agent?"

While our conclusions are based on the study of only 200 patients, we believe that these results merit publication at this stage because of their implication. This study will continue until at least 200 patients have been studied in each group.

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Vaginal microbial flora in normal young women

M J GOLDACRE, B WATT, NANCY LOUDON, L J R MILNE, J D O LOUDON, M P VESSEY

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Summary and conclusions

Vaginal swabs were taken from 1498 women attending a family planning clinic. The flora was assessed in the absence of any information about the women to whom the swabs related. Yeasts and fungi were present in 311 women (21%) and were no more prevalent among "pill" users than others. Candida albicans was significantly associated with vulval itching and with a vaginal discharge described as heavier than normal or curdy on clinical examination, though these abnormalities were present in only a minority of women with the organism. Trichomonas vaginalis was found in 14 women (1%) and was associated with abnormalities of vaginal discharge in all but one. Gram-negative anaerobic bacilli were significantly more common in women with a troublesome vaginal discharge and those who used an intrauterine device than others. No associations were found between fungi other than C albicans or the other bacteria sought and either symptoms or clinical abnormalities of vaginal discharge.

Introduction

Information about the normal vaginal flora is needed when assessing the pathogenic role of organisms in women with genito-urinary symptoms. The vaginal flora has often been studied in selected patients—for example, in women with vaginal discomfort or discharge,[1-3] in women attending venereology clinics,[4 5] in patients before gynaecological operations,[6 7] and in pregnant women.[8 9] Studies on normal women have, however, been fewer and usually based on small numbers.[10-12] We have therefore studied the vaginal flora in 1498 women, who were unselected except that they sought contraceptive advice from a family planning clinic.

Department of Social and Community Medicine, University of Oxford, Oxford OX1 3QN
M J GOLDACRE, BM, MFCM, lecturer
M P VESSEY, MD, MRCP, professor

Western General Hospital, Edinburgh EH4 2XU
B WATT, MD, MIBIOL, consultant microbiologist
L J R MILNE, BSC, PHD, principal mycologist

Edinburgh Family Planning Centre, Edinburgh EH4 1NL
NANCY LOUDON, MB, medical co-ordinator, family planning services

Eastern General Hospital, Edinburgh EH6 7LN
J D O LOUDON, FRCS, FRCOG, consultant obstetrician and gynaecologist

Patients and methods

The study was conducted at the Edinburgh Family Planning Centre between October 1975 and March 1977. Women were included if they were either new patients or repeat attenders who had not been seen at the clinic for at least six months. The clinical methods (including questions used to elicit symptoms) are described elsewhere.[13] In brief, characteristics of the women (including symptoms if any) were recorded by a research nurse using a structured questionnaire. Each woman was then examined by a doctor who, to avoid bias, was not provided with any medical history. Findings on vaginal examination were recorded on a structured check list. Albumin-coated swabs (Exogen) were taken from the external cervical os of all women, from the vaginal fornix of all women in whom the vaginal discharge was considered to be abnormal in either quantity or consistency, and from the fornix of a sample of 145 women with no abnormal vaginal discharge. Duplicate swabs were taken from each site under direct vision through a speculum. Care was taken to minimise the possibility of contaminating a swab from one site with material from another.

For each specimen one of the duplicate swabs was broken off into Stuart's transport medium (Oxoid). The other was streaked over one-third of the surface of a plate of Phillips selective medium and then broken off into trichomonas medium (Oxoid). Specimens were kept at room temperature until arrival at the laboratory, where they were used to inoculate, respectively, plates of blood agar, MacConkey's medium and neomycin blood agar (from the transport medium), and malt-peptone agar (from the trichomonas medium). The neomycin blood agar plate and one blood agar plate were incubated anaerobically in 90% hydrogen plus 10% carbon dioxide. The other blood agar plate and the plate of MacConkey's medium were incubated aerobically.

The flora was assessed in the absence of any information about the women to whom the swabs related. Full details of culture media, isolation procedures, and definitions used are available on request (to MJG) and will be given elsewhere. Only the predominant colony types were noted: very small numbers of other types of colony (except those on Phillips selective medium for *Neisseria gonorrhoeae*) were ignored.