

PROPHYLAXIS OF DEEP VENOUS THROMBOSIS AFTER ACUTE ABDOMINAL OPERATION

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Two hundred and forty-five patients who underwent acute extensive abdominal operations were randomized into three regimens to achieve optimal prophylaxis of postoperative thromboembolic complications. All of the patients were screened by the ^{125}I -fibrinogen uptake test for seven days and if the phlebographic findings were positive. Of 81 patients receiving low dose heparin, 12 had thromboembolism. Of 79 receiving a combination of low dose heparin and graded compression stockings, two had thromboembolism, and of 85 receiving a combination of dextran and graded compression stockings, 13 had this complication. This difference is significant in favor of the second treatment ($p=0.013$). It is concluded that the combination of low dose heparin and graded compression stockings is an effective way to prevent thromboembolism after acute abdominal operations.

THE INCIDENCE of postoperative thromboembolic complications (TE) after an elective abdominal operation can be substantially lowered by using different prophylactic regimens (1). Low dose heparin has gained wide acceptance and is now used by many surgeons (2, 3). Combination prophylaxis is documented as being even more effective (4), and its use is increasing in Denmark (3).

The efficacy of prophylaxis in acute abdominal operation has, to our knowledge, never been investigated systematically, although it is thought that acutely ill patients might have a higher risk of having postoperative TE than patients who underwent elective operations (5). This study was done to evaluate the incidence of TE in patients undergoing acute extensive abdominal operations when using three different methods of prophylaxis.

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MATERIALS AND METHODS

Between July 1986 and August 1988, 276 patients undergoing acute abdominal operations entered the study provided they fulfilled at least one of these risk factors: more than 39 years of age, malignant lesions suspected, varicose veins, cardiac disease or hypertension, diabetes mellitus, obesity or earlier thromboembolic episodes. The operation had to be considered to last for more than one hour. Patients were excluded if any of these findings were present: allergy to iodine, dextran or heparin use; hepatic or untreated cardiac failure; severe peripheral arterial insufficiency; pregnancy or bleeding in the gastrointestinal tract. Informed consent was obtained, and the study was approved by the local ethics committee. The operation was defined as acute if it was considered to be immediately life-saving or was performed ahead of the planned operative program of the department to lower the morbidity for the patient. This series was not consecutive because of capacity problems and the fact that one of the participating departments was closed during the investigation period.

To begin prophylaxis preoperatively, the patients were randomized when the indication for acute operation was established to three different prophylaxis methods by means of continuous random numbers placed in sealed envelopes. Those in the low-dose heparin group received 5,000 units of sodium heparin (Noparin[®]; Novo A/S, Copenhagen, Denmark) administered subcutaneously preoperatively and continued twice daily for seven days or until the patient was fully mobile. In the group receiving low-dose heparin and thigh length graded compression (TED) stockings, 5,000 units of sodium heparin were given in combination with TED-stockings[®] (Kendall) measured for each patient, applied preoperatively and worn day and night until full mobilization occurred. In the dextran and TED-stockings group, MacroDEX 70[®] (dextran) (Kabi-Vitrum A/S, Copenhagen, Denmark) was given

TABLE I.—WITHDRAWAL OF PATIENTS

	Groups		
	1	2	3
	LDH/ LDH, n=84	LDH/ TED, n=94	DEX/ TED, n=98
Operation cancelled	0	1	1
Informed consent withdrawn	0	0	2
Clerical errors*	0	4	2
Early postoperative death†	3	8	4
Incorrect administration of drug	0	2	4
Patients evaluated	81	79	85

*Incomplete observation because of lack of fibrinogen scans or phlebography, side effects or wrong allocation protocol.

†Death within 48 hours with no evidence of thromboembolism.

LDH, Low-dose heparin; LDH/TED, low-dose heparin plus graded compression stockings; and DEX/TED, dextran plus graded compression stockings.

as a 500 milliliter infusion intraoperatively and repeated on the first and third postoperative days combined with TED-stockings as mentioned in the former group. To avoid anaphylactic reactions, 20 milliliters of Promiten® (a low molecular dextran) (KabiVitrum A/S, Copenhagen, Denmark) was given intravenously just before the dextran infusion was administered.

To detect deep venous thrombosis (DVT), all patients were screened with the ¹²⁵I fibrinogen uptake test (FUT). After blocking the thyroid gland with intravenous sodium iodine, 100 microcuries of ¹²⁵I labeled fibrinogen (Amersham, United Kingdom) was injected intravenously preoperatively and scintimetry was performed on the first, third, fifth and seventh postoperative days and evaluated according to the criteria of Olsson (6). Whenever indicative of DVT, the FUT was followed by ascending phlebography. If any patient had signs of DVT, ascending phlebography was performed irrespective of the outcome of FUT. If patients had signs or symptoms of pulmonary embolism (PE), perfusion pulmonary scintigrams combined with roentgenograms of the chest were performed. Follow-up studies of the records for all patients were done 30 days postoperatively to detect late death from TE, and whenever possible, an autopsy was performed.

There were several criteria for diagnosing TE. These included either DVT demonstrated as intraluminal filling defects at phlebography, PE demonstrated as perfusion defects at pulmonary scintigraphy combined with normal ventilation demonstrated at roentgenograms of the chest, obvious clinical signs of DVT in patients with positive FUT but where phlebography was not available, or TE demonstrated at autopsy.

For statistical evaluation, the Kruskal-Wallis test was used for continuous data, and the chi-square

TABLE II.—PATIENT CHARACTERISTICS

	Groups		
	1	2	3
	LDH, n=81	LDH/ TED, n=79	DEX/ TED, n=85
Male to female ratio	28/53	30/49	31/54
Median age, yrs.	70.7	72.0	72.1
Range, yrs.	37 to 91	40 to 95	42 to 92
Median duration of operation, hrs.	6.2	5.9	6.1
Range, 1/4 hr.	3 to 28	3 to 17	3 to 14
Biliary tract operations	20	15	13
Gastric operations	16	13	10
Small intestine operations	9	16	17
Colorectal operations	16	17	18
Appendicitis	7	5	11
Miscellaneous*	13	13	16

*Explorations, incarcerated hernias, salpingitis and pancreatitis.

LDH, Low-dose heparin; LDH/TED, low-dose heparin plus graded compression stockings; and DEX/TED, dextran plus graded compression stockings.

test for binominal data. The incidence of TE was stratified according to the type of operation performed and evaluated by means of a Mantel-Haenszel test. Patients were considered eligible for evaluation if they attended at least three days observation postoperatively or died from TE within the first two days. Only patients who completed the prophylaxis treatment were evaluated.

RESULTS

Two hundred and seventy-six patients entered the study, but 31 were subsequently withdrawn because of the reasons given in Table I. Fifteen patients died within a 48 hour period after operation. There was no suspicion of TE. Two of three, four of eight and two of four patients in the three groups had autopsy performed. The reasons for death were mainly septicemia, mesenteric arterial thrombosis or cardiac failures.

With regard to age, sex and duration of operation, the patients were equally distributed among the three groups (Table II), as were the number and distribution of inclusion factors. There were more (not significant) biliary operations in group 1 and more (not significant) appendicitis in group 3. Sixty-two patients were not screened during all of the planned seven days because of early postoperative mobilization and discharge from the department (median observation five days, range of three to six days). These patients were equally distributed among the groups, according to number and observation time and were included in the study. None had TE develop, and none died within the first 30 days.

In the first one-half of the study, more patients than expected with stockings had positive FUT

TABLE III—INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH DIFFERENT ACUTE ABDOMINAL OPERATIONS

	Groups		
	1, LDH	2 LDH/TED	3 DEX/TED
Biliary tract operations	2/20	1/15	2/16
Gastric operations	2/16	0/13	1/10
Small intestine operations	2/9	0/16	4/17
Colorectal operations	4/16	1/17	3/18
Appendicitis	1/7	0/5	1/11
Miscellaneous	1/13	0/17	2/16
Total	12/81 (15)	2/17 (3)	13/85 (15)

LDH, Low-dose heparin; LDH/TED, low-dose heparin plus graded compression stockings, and DEX/TED, dextran plus graded compression stockings.

Chi-square for total study, 8.58; degree of freedom, 2, and $p=0.013$.

After stratification for type of operation, Mantel-Haenszel test—1 versus 2; chi-square of 6.21; degree of freedom 1, and $p=0.013$. Mantel-Haenszel test—2 versus 3; chi-square of 9.63; degree of freedom 1, and $p=0.002$.

Numbers in parentheses are percentages.

with no DVT at phlebography. As the FUT-scintimetries were performed with the stockings in situ and the 125 Iodine is known to be eliminated by the kidneys, the reason for these many false-positive FUT was found to be the result of pollution of urine at the stockings. After excluding this possible bias, only two false-positive findings for FUT were noted. For this reason, evaluation of positive FUT findings is not included in the results.

Because of the condition of one patient in group 1, phlebography was not done despite positive FUT findings. This patient was considered as having TE since obvious clinical signs were present. In group 3, two patients did not undergo phlebography despite positive FUT results. One patient was included as having TE because of obvious clinical signs. The other was excluded because there were no signs of DVT and phlebography was refused.

One patient in group 1 and one patient in group 2 had a primarily normal FUT and obvious signs of DVT at 28 and 14 days postoperatively, which was verified at phlebography. In group 3, one patient was readmitted with clinical symptoms of PE at follow-up study done the 30 days postoperatively. This was verified at pulmonary scintigraphy. The primary FUT was normal. These three patients were included in the study as having TE.

In the three groups, 11, 16 and 17 patients died within 30 days. The frequency of autopsy was eight of 11, 11 of 16 and ten of 17, and none of the patients who died were suspected of suffering from TE. One patient in group 2 died of PE on the 14th postoperative day, but

had earlier been excluded on the second day because the stockings had been removed.

The incidence of TE in the three groups is listed in Table III. Only one patient was classified as having TE because of PE (the patient in group 3 with late PE). Because of the skewness in the types of operations performed in the three groups, the patients were stratified according to the type of operation. The distribution of TE favored patients who underwent operations upon the large or small intestines (14 of 93) compared with all other operations (13 of 152), but the difference was not significant ($p>0.1$). The stratification did not alter the results when the three groups were compared as a whole. The group of patients receiving the combination of low dose heparin and graded compression stockings had a significantly lower incidence of TE compared with the two other groups.

In one patient, extensive postoperative bleeding occurred. Dextran was withdrawn, but the patient had to be reoperated upon and the reason for bleeding was considered surgical. The median incidence of perioperative bleeding and the number of transfusions required are listed in Table IV. More postoperative transfusions were given to those in the dextran group. The difference was not significant.

DISCUSSION

It was thought that acute abdominal operations are a specific risk factor for developing TE (5). In this study, in which all patients received prophylaxis, the incidence of TE in the two groups receiving heparin did not exceed the incidences described in an investigation on elective abdominal operations (4). It is known that prophylaxis for patients with acute conditions is not used to the same extent as for patients undergoing elective treatment (3). In many situations, the prophylaxis is first prescribed during or after operations (unpublished experience) and this might be too late, as it is an established fact that the process of thromboembolism begins during the operation in many instances (7), and in those with acute conditions, maybe even preoperatively. The need for precise and effective regimens is obvious, but such regimens have never been properly investigated, perhaps because of the many methods and practical problems with prospective studies in this group of patients.

In this investigation, we have evaluated three regimens, which are known to protect against

postoperative TE in elective operations (1, 4, 8, 9), the combination therapy being superior to monotherapy (4, 8, 9). We found that the combination of low-dose heparin and graded compression stockings is superior to the other regimens investigated. It is known that local stasis in combination with activated clotting factors are thrombogenic (10), and when the graded compression stockings increase the venous blood flow velocity in the lower venous tree (11), there is a good theoretic explanation for our findings.

Dextran and stockings do not seem to be an acceptable choice for thromboprophylaxis in this group of patients, even when combined with stockings. This is somewhat surprising, as the combination of dextran and graded compression stockings has been found to be superior to dextran in elective general surgical treatment (9), and dextran alone is effective in general operations (12). The use of dextran is considered good prophylaxis in acute orthopedic operations (12), when the hemostatic mechanism is activated preoperatively, which is also thought to be true in acute abdominal operations. The optimal prophylaxis of DVT seems to be different in acute general and orthopedic operations and perhaps the effect of dextran is linked to special unknown factors released from fractures. It is well known that thrombi established during dextran treatment undergo lysis more easily (13), and thus, do not embolize. This can explain the contradiction that we discovered many thrombi in the dextran group, while dextran is known to prevent fatal pulmonary embolism with an efficacy equal to low-dose heparin (14). The number of patients included in this study is too low to evaluate the efficacy of the investigated regimens in preventing fatal PE.

Only a few and rather small studies (15) have dealt with thromboprophylaxis in acute abdominal operations. In the largest series, the incidence of DVT after dextran prophylaxis was four of 31 and after dextran and dihydroergotamine, two of 20. These figures are similar to the results in the dextran treated group in our study.

One of the problems in studies dealing with thrombosis prophylaxis is that, to achieve precise results, all of the patients have to be treated with the same care and observed over the same period of time. These design demands were not totally fulfilled in this study, although this was the intention. First of all, a group of patients was discharged before termination of the planned

TABLE IV.—BLEEDING COMPLICATIONS

	Groups		
	1 LDH, n=81	2 LDH/TED, n=79	3 DEX/TED, n=85
Median perioperative blood loss	199.6	200.3	200.3
Range, ml.	0 to 5,000	0 to 4,000	0 to 5,500
Total number of perioperative transfusions	36	39	40
Total number of post-operative transfusions	18	19	28

LDH, Low-dose heparin; LDH/TED, low-dose heparin plus graded compression stockings, and DEX/TED, dextran plus graded compression stockings.

seven day screening period, but they were equally distributed among the three groups. They were all discharged early because of an uneventful postoperative course, and no one died within 30 days. If these patients should be excluded, it would only strengthen the conclusions of our study, but it would not reflect the daily routine in a general surgical department.

Three patients (one patient in each group) were classified as thromboembolic patients because of "late" TE despite normal FUT during the observation period. We find that it would be a greater bias to exclude these patients thereby masking the total incidence of postoperative TE. If we had chosen an observation period of strictly seven days only in all patients, this would not have changed the statistical strength of the investigation (chi-square equals 9.19; degree of freedom equals 2; $p=0.01$). With these facts in mind, we do not find that the bias contained in the dissimilar observations of this group of often quite sick, elderly surgical patients with a high operative mortality rate can substantially modify our conclusion.

The type of operation did not influence the incidence of TE significantly. A tendency, however, was present, as patients who underwent operation upon the intestine had more TE than other patients. Patients with acute intestinal obstruction and perforated colon comprised a group of patients with a more severe illness than patients with appendicitis or perforated ulcer, which might explain this difference. The stratified analysis could not define any influence of the type of operation performed on the difference in incidences of TE in the three groups.

Investigation of the prevention of complications in acute abdominal surgical patients is extremely difficult to perform because of the heterogeneity of patients and their postoperative course. The

many possible biases contained in this investigation have to be taken in mind, but we find that the most serious instances were excluded and that the remaining cannot substantially modify our final conclusion that can be taken as a guideline in the daily routine.

The use of low-dose heparin and graded compression stockings is an effective regimen to prevent postoperative DVT after acute abdominal operations when used routinely in all emergency operations done on the gastrointestinal tract except for instances of bleeding. It is more effective than low-dose heparin alone or the combination of dextran and graded compression stockings.

SUMMARY

Prophylaxis against postoperative TE in patients undergoing acute abdominal operations has not previously been investigated. Three different regimens were evaluated in 245 patients scheduled to undergo emergency operations. Randomization was carried out before the operations and the patients were screened with ^{125}T -fibrinogen uptake test for seven days. Whenever indicative for DVT, venography was performed. Of 81 patients receiving low-dose heparin, 12 had TE. Of 79 receiving a combination of low-dose heparin and graded compression stockings, two had TE, and of 85 receiving a combination of dextran and graded compression stockings, 13 had TE. This difference is significant in favor of this second treatment ($p=0.013$). It is concluded that the combination of low-dose heparin and graded compression stockings is an effective way to prevent TE after acute abdominal operations.

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