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Urological Research

The Effects of Low-Dose Heparin Treatment on Patients Undergoing Transvesical Prostatectomy

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Summary. Post-operative venous thrombosis, blood loss and pre- and post-operative plasma heparin concentrations were studied in a prospective double blind trial with low-dose heparin therapy in 59 patients undergoing transvesical prostatectomy. Thrombosis rate, diagnosed with the ^{125}I-fibrinogen method, was significantly reduced in the first 5 post-operative days, i.e. during but not after the period of heparin therapy. One patient who developed major thrombosis in spite of heparin prophylaxis is presented. Heparin therapy did not increase average blood loss, but was suspected to be the cause of severe bleeding in 1 patient, who may have had a latent hemorrhagic diathesis. Plasma heparin levels were significantly raised during heparin therapy, and were significantly lower in both heparin and placebo treated patients on days when thromboses started.

Key words: Subcutaneous heparin, Plasma heparin concentration, Transvesical prostatectomy, Post-operative thrombosis, Haemorrhage.

INTRODUCTION

Treatment with small subcutaneous doses of heparin started 1-2 h before operation has been widely accepted as safe prophylaxis against post-operative venous thrombosis (6, 7, 10). Although this treatment has been considered free from serious complications, some authors have claimed that it may lead to fatal bleeding in a few cases (9).

The aim of the present investigation was to study the effect of low doses of heparin treatment on pre- and post-operative bleeding, and on the incidence of venous thrombosis in patients undergoing suprapubic prostatectomy, and the correlation between these 3 factors and plasma heparin concentration.

MATERIAL AND METHODS

Fifty-nine consecutive patients, with a mean age of 68 (54-81) years, were included in the study. Patients who were taking oral anticoagulants were excluded from the trial. No patient had a history of haemorrhagic diathesis. The patients were instructed not to take aspirin or any other drug that might influence haemostatic mechanisms for at least 1 week before admission. This regime was maintained during the hospital stay.

All patients underwent transvesical enucleation of benign prostatic hyperplasia according to a standard operative procedure, and had suprapubic as well as urethral bladder drainage with continuous irrigation of the bladder during the first 15-20 post-operative hours.

All patients were given tranexamic acid (Cyklokapron^{R}, Kabi) - 1 g intravenously twice on the day of operation, starting 30 min after the end of operation, and 1 g orally three times a day from the 1st to the 6th post-operative days.

Measurement of Blood Loss

For 72 h from the beginning of the operation, the contents of all aspirators, urine bags, bladder irrigations and all blood-stained dressings, swabs and bandages were collected. The blood was washed out from cloth and bandages by hand in tap water. The mixture of blood, urine and washing fluid in tap water was collected for four different periods, per-operatively and then for the first 3 post-operative 24 hour periods. The vol-

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ume was measured and the solution well mixed. Five ml of this solution was mixed with 25 ml of 2.5 mol/l sodium hydroxide and the absorbance was read in a Beckman B spectro-photometer at 545 nm against a blank of 2.5 mol/l sodium hydroxide (3).

Prophylaxis of Thrombosis

Each patient was assigned a coded package containing ampoules of 1 ml sodium heparin (Vitrum, Stockholm) in a concentration of 5 000 IU/ml or 1 ml of physiological saline (placebo). One ml of heparin or placebo was given subcutaneously starting 1 h before the operation. After the operation, up to and including the 5th post-operative day, the first 21 patients were given 1 ampoule every 12 h and the last 38 patients 1 ampoule every 8 h. If no complications occurred the code was not broken until blood loss calculations and screening for thrombosis were completed. It was found that 30 patients had received heparin and 29 placebo.

Diagnosis of Thrombosis

Thrombosis was diagnosed by the ^{125}I-fibrinogen method with criteria used by Hedlund (5). Scanning was done pre- and post-operatively on the day of operation and on the 1st, 2nd, 3rd, 4th, 7th, 9th and 10th post-operative days. No screening was performed for pulmonary embolism.

Measurement of Plasma Heparin Concentration

The heparin concentration in plasma was measured in the last 30 patients by the method of Teien et al. (11) as modified by Blombäck and Hedlund (2). Samples were taken in the morning 3 days prior to the operation and before (test A) and 2 h after (test B) a subcutaneous injection of 5 000 IU sodium heparin. Further samples were taken on the morning of operation before heparin or placebo was given, then immediately after the operation (i.e. 2-3 h after the pre-operative injection of heparin or placebo) and on the mornings of the 1st, 2nd, 3rd, and 4th post-operative days 2 h after the subcutaneous injection of 5 000 IU of heparin (or placebo) and on the morning of the 10th post-operative day.

The laboratory assistant performing the heparin assays was not aware of the result of thrombosis screening or blood loss or to which treatment group the patients belonged.

Statistical Methods

Statistical evaluations were carried out with Student's t-test and the chi-2-test.

RESULTS

There was no significant difference in blood loss during the 4 different periods between patients receiving placebo or heparin given as 5 000 IU either 2 or 3 times daily (Table 1). One patient in the heparin group was re-operated on the 1st post-operative day because of bleeding. His code was broken, heparin therapy stopped and he was taken out of the trial on the 1st post-operative day. More detailed data of this patient is seen in Fig. 1. One patient in the placebo group was re-operated in the evening of the operation day because of bleeding. The patient was a poor risk and 4 weeks later died from a pulmonary embolism and cardiovascular insufficiency. Another patient in the placebo group developed a bowel obstruction which necessitated operation on the 3rd post-operative day. These 2 last patients were taken out of the trial when intensive care treatment including heparin therapy was started.

Six of the 29 patients in the heparin group developed thrombosis during the first 10 post-operative days (Table 2) compared to 13 of the 28 patients in the placebo group ($p > 0.05$). During the period of heparin therapy (5 days), only 2 patients in the heparin group against 11 placebo patients developed thromboses ($p < 0.0005$). Two patients in the placebo group and one in the heparin group developed thromboses considered to be potentially dangerous i.e. able to develop major pulmonary embolism because of involvement of thigh veins. After termination of thrombosis prophylaxis, new thromboses were detected in 4 heparin and 2 placebo patients. These thromboses

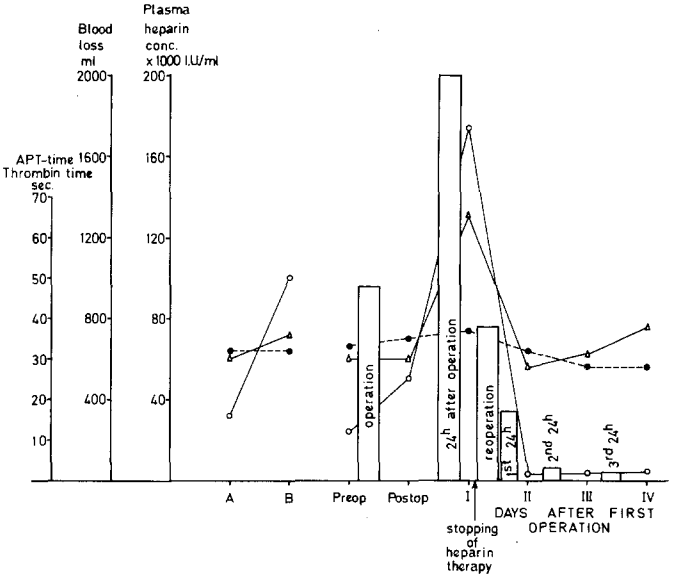

Fig. 1. Coagulation parameters and blood loss □ (ml) in a patient reoperated because of bleeding. Plasma heparin concentration (I.U./ml x 1000) o—o; thrombin time (s) Δ - Δ; APT-time (s) ●---●

Table 1. Blood loss (ml) during and after prostatectomy

Patient groups	Number of patients	Per-operative	Post-operative 24 h periods I	II	III
First part - heparin given twice daily					
heparin group	10	601±344	186±218	39±38	44±42
placebo group	11	632±469	205±241	55±33	27±19
Second part - heparin given three times daily					
heparin group	20	547±295	307±451	46±45	27±22
placebo group	18	563±395	271±279	40±38	29±32
First and second part together					
heparin group	30	565±308	267±389	44±44	33±30
placebo group	29	590±417	247±263	46±37	28±28

Table 2. Post-operative venous thrombosis (number of patients with bilateral thrombi)

	Heparin group n = 29	Placebo group n = 28	p Student's t-test
Patients with thrombosis within the first 10 post-operative days	6(2)	13(6)	>0.05
Patients with thromboses detected during the first 5 post-operative days (when heparin/placebo was given)	2(1)	11(3)	<0.0005
Patients with thromboses detected only after the 5th post-operative day	4(1)	2(1)	>0.05
Patients with small lower leg thromboses, uni- or bilateral, occupying only 1 position for scanning detector	5(1)	7(2)	>0.05
Patients with thigh-vein thromboses	1(1)	2	>0.05

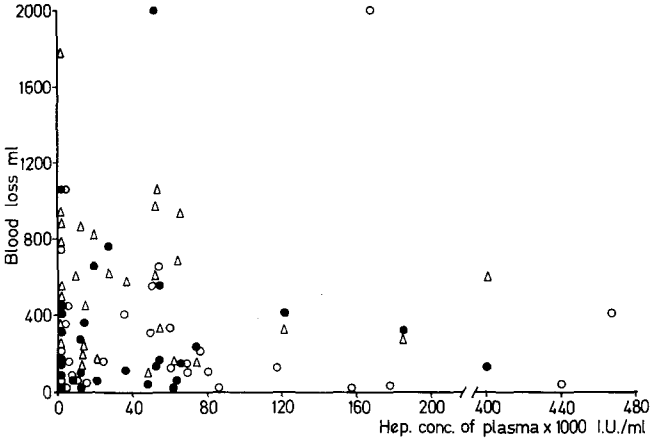

Fig. 3. Correlation between blood loss and plasma heparin concentration. Heparin level at the end of operation to blood loss during operation Δ and during the first 24 post-operative hours ●. Heparin level in the morning after operation to blood loss during the first 24 post-operative hours o

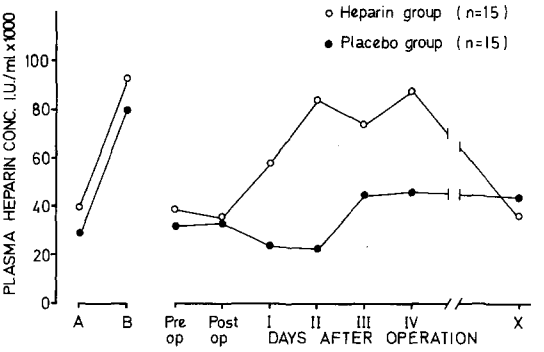

Fig. 2. Plasma heparin concentration in connection with operation, 3 days prior to operation (test A) and 2 h after test B, a subcutaneous injection of 5000 IU sodium heparin

were all small occupying only 1 scanning position, and were bilateral in 1 patient of each group. One patient of the heparin group developed bilateral lower leg thromboses during heparin treatment which progressed into the thigh on the 7th to 9th day. He was given full-dose anticoagulant therapy with heparin and dicoumarol and taken out of the trial from the 9th post-operative day.

Plasma heparin concentration (Fig. 2) was higher in the heparin treated group but the difference is statistically significant only on the 2nd post-operative day ($p < 0.0005$). Mean values in heparin and placebo patients during heparin treatment, i.e. tests taken from the end of operation up to the 4th post-operative day are seen in Table 3a. Four patients had very high heparin levels in the tests taken on the morning after operation which also can be seen in Fig. 3. A repeat of these tests on stored samples did not reveal any technical faults. We do however suspect that something may be wrong with these samples. It may be, that these 4 patients received extra heparin by mistake, during their stay in the post-operative ward the first night after operation in saline-heparin solutions used routinely in this department to clear intravenous catheters. These 4 values have therefore been excluded in the following calculations including those in Fig. 2. There is still a significant difference between samples taken without and with heparin therapy (Table 3b). We have also studied heparin levels at the time of development of thrombosis, i.e. those heparin samples taken most closely to the day when the first signs of increased radioactivity were seen on leg scans in those regions, where on consecutive scans thromboses later developed (5). Seventeen of these 21 samples were taken within 24 h of this first sign of a thrombosis. The remaining 4 thromboses started on days when heparin samples were not collected. In Table 3c it can be seen that heparin levels on days when thromboses developed were signifi-

Table 3a-m. Plasma heparin concentration

	I. U. /ml	No. of patients	No. of samples
a. All samples during heparin/placebo treatment			
Heparin group	0.086±0.088	15	75
Placebo group	0.036±0.042	15	73 ***
b. All samples during heparin/placebo treatment - suspected false values omitted			
Heparin group	0.071±0.052	15	72
Placebo group	0.036±0.042	15 *	71 ***
Samples most close to the development of thrombosis on scan vs all post-operative samples in patients without thrombosis			
c. Whole series			
with thrombosis	0.024±0.030	14	21
without thrombosis	0.067±0.051	16 **	93 ***
d. Heparin group			
with thrombosis	0.034±0.044	5	7
without thrombosis	0.077±0.049	11	56 *
e. Placebo group			
with thrombosis	0.018±0.021	9	14
without thrombosis	0.049±0.050	6	35 *
Average of all post-operative samples			
f. Whole series			
with thrombosis	0.032±0.038	14	77
without thrombosis	0.066±0.051	16	91 ***
g. Heparin group			
with thrombosis	0.038±0.042	5	26
without thrombosis	0.077±0.049	11	56 ***
h. Placebo group			
with thrombosis	0.028±0.036	9	51
without thrombosis	0.049±0.050	6	35 *
Mean of two pre-operative samples without preceding heparin injection			
k. Whole series			
with thrombosis	0.019±0.026	14	27
without thrombosis	0.047±0.047	16	32 **
l. Heparin group			
with thrombosis	0.020±0.034	5	9
without thrombosis	0.046±0.044	11	22
m. Placebo group			
with thrombosis	0.018±0.021	9	18
without thrombosis	0.050±0.052	6	11 *

*p<0.05
**p<0.01
***p<0.001

cantly lower than the mean value of all post-operative tests taken on patients who never got a thrombosis. Corresponding calculations within the heparin and placebo group (Table 3d-e) gave significant differences of a lower degree. Even the average of post-operative values in patients developing thromboses were significantly lower than those of patients not developing thromboses (Table 3f-h). The possibility of predicting post-operative thromboses from low pre-operative heparin levels is illustrated in Table 3k-m with significant results for the whole series and for the placebo group.

Comparison of groups of samples from different patient categories (Table 3) gave highly significant differences, much of which however disappeared when calculations were made using the number of patients instead of the number of samples. Plasma heparin levels varied much between patients and also from day to day in the same patient as was also found by Kakkar et al. (7).

Although patients developing thromboses had mostly low levels of heparin, it was not possible to find a way by daily heparin analyses in the post-operative period to predict thrombosis

in the individual patient.

Blood loss during operation and during the first post-operative 24 hour period could not be correlated to plasma heparin levels seen immediately after the operation and on the morning after the operation (Fig. 3).

DISCUSSION

In spite of a rather wide but expected scatter of values for blood loss within both the placebo and heparin groups, the average values were strikingly similar in the 2 patient groups and equal to other reports of transvesical prostatectomy (1, 4). Some patients had markedly high levels of heparin in plasma without severe bleeding (Fig. 3).

The patient in the heparin group, re-operated because of bleeding, had no history of haemorrhagic diathesis, intake of aspirin or other drugs as a cause of bleeding. On the day of haemorrhage his heparin level was 0.167 IU/ml and there was a corresponding rise in thrombin-time (Fig. 1). Bleeding was never copious in this patient but after stopping heparin therapy, before reoperation, per- and postoperative blood loss and coagulation parameters became normal (Fig. 1). At re-operation diffuse bleeding from the prostate cavity was found, without any bleeding arteries as the main cause of haemorrhage. A control 16 months after the prostate operation revealed factor VIII concentration of 61-63% and a Normotest value of 75%. It was found that these tests had been similarly low before the prostate operation. This patient is considered to have had a latent haemorrhagic diathesis and that low dose heparin therapy probably had induced bleeding. It did not seem possible to definitely select this patient as at risk from bleeding since other patients had similarly low levels of factor VIII and Normotest or even higher levels of plasma heparin without bleeding. The placebo patient, who was re-operated because of bleeding, did not have abnormal coagulation parameters. His plasma heparin level was not measured. Post-operative thromboembolism was not too dramatic in this trial. With the exception of the placebo patient, re-operated because of bleeding, who died from pulmonary embolism and cardiac insufficiency after 4 weeks in the intensive care unit, there were no pulmonary emboli big enough to cause clinical signs. This may be due to the fact that patients with thrombi in the thighs were given anticoagulant therapy. Most patients had small uni- or bilateral thromboses occupying only one point of scanning.

One patient in the heparin group did however develop bilateral lower leg thromboses on the 2nd and 3rd post-operative day respectively. These thromboses grew within the lower legs during heparin therapy and after this had been stopped, on the 5th post-operative day, they extended into the proximal thighs. Anticoagulant therapy was instituted and his course was thereafter uneventful. This patient had a short cardiac arrythmia on the night following operation but no other per- or post-operative complication or other evident reason for this thrombotic spread. In fact he had the most extensive thrombotic complication of the whole series and resembles a patient in the material of Kruse-Blinkenberg et al. (8) who developed fatal pulmonary embolism during low-dose heparin therapy. These 2 respresent a probably small group of patients who need to be recognized prior to the development of major thromboembolism. The plasma heparin levels of our patient were not low enough to distinctly select him from the other patients, but he did also have very low pre- and post-operative levels of antithrombin III.

Low-dose heparin therapy dramatically reduced the incidence of small lower leg thromboses in the early post-operative period. However, it failed to prevent the development of major potentially dangerous thrombi in 1 patient after cessation of heparin treatment. Prolonged thrombosis prophylaxis has been recommended by some authors, but a simple way to recognize the relatively few patients in need of that therapy, without routine isotope scanning, remains to be found. In this trial as in that of Sagar et al. (10) there was some correlation between thromboses and low heparin levels in post-operative (Table 3c-e) and even pre-operative (Table 3 k-m) samples but this was not true for all individual thromboses. Further analyses of our results including antithrombin III and other coagulation parameters will be published elsewhere.

The heparin assay (11) measuring heparin concentration mainly as anti-Xa activity seemed to have very good reproducibility and obviously gave higher values than the method of Yin (12). Our values after sodium heparin therapy were considerably higher than those of Sagar et al. (10) using calcium heparin in connection with total hip replacement, and more comparable to those of Kruse-Blinkenberg et al. (8) who also used the method of Teien. Plasma heparin levels are probably closely related to the magnitude of operation. The large inter- and intra-individual variations of plasma heparin levels after low-dose heparin therapy noted by Kakkar et al. (7) and in this trial warrant further studies.

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