Acta orthop. scand. *53*, 937–945, 1982

DEEP VEIN THROMBOSIS FOLLOWING HIP SURGERY

Relation to Activated Factor X Inhibitor Activity: Effect of Heparin and Dextran

T. WELIN-BERGER, S. BYGDEMAN & C. MEBIUS

Departments of Orthopaedic Surgery, Clinical Physiology and Anaesthesiology, St Göran's Hospital, Stockholm, Sweden

Activated factor X inhibitor (FXaI) activity was measured with a newly developed method during operation and during the postoperative period in 60 patients undergoing total hip replacement. The patients were randomly allotted to three groups. In two groups the effect of prophylactic treatment with dextran and low dose heparin were evaluated, while the third group served as a control. Postoperative deep vein thrombosis was diagnosed with plethysmography and venography and related to observed changes in inhibitor activity. The frequency of deep vein thrombosis was found to be 25, 47 and 33 per cent in the three groups respectively. With the test system for measurements of FXaI-activity which made it possible to determine both the overall ability of the plasma to neutralize FXa and the activity independent of any accelerator or antagonist of XaI-activity, it was possible to demonstrate inhibitor consumption in all groups including the heparin treated group where the overall inhibitor activity was increased. A marked decrease in inhibitor activity was usually observed in the patients developing postoperative thrombosis in the control group, while in the other groups the relationship was less clear.

Key words: dextran; FXaI-activity; heaprin; hip surgery; thrombosis

Accepted 16.v.82

The most important inhibitor of blood coagulation is an α_2-globulin, which inhibits both thrombin and activated factor X and which has variously been named antithrombin III, activated factor X inhibitor (FXaI) or heparin cofactor (Yin et al. 1971). It is well known that patients with an inherent deficiency of antithrombin III are susceptible to venous thrombosis (Egeberg 1965, Abildgaard 1968, Marcinial et al. 1974). Several reports have also demonstrated reduced FXaI-activity in patients with acute deep vein thrombosis and in patients developing postoperative thrombosis (Sagar et al. 1976, Lechner et al. 1979, Stamatakis et al. 1977). In some studies, however, no relationship has been found between antithrombin III and tendency to thrombosis. This discrepancy might be due to the fact that antithrombin III has in these studies been determined by an immunoelectrophoretic technique which does not provide information of the biological function of the antigen (Hedner & Nilsson 1973, Sas et al. 1974) or by a clotting assay measuring the specific antithrombin activity rather than the anti-factor Xa effect (Korwald et al. 1974, Bergström & Lahnborg 1975).

Why patients with decreased FXaI-activity develop thrombosis is still unknown. Presumably the body is dependent on near normal values of the inhibitor to counteract intravascular coagulation. During and after surgery a "hypercoagulable state", previously not present, is created in some individuals. It is conceivable that this

0001-6470/82/060937-09 $02.50/0

hypercoagulability will remain nonthrombotic as long as the rate of neutralization of factor Xa exceeds that of factor Xa activation. However, if the rate of factor X activation is faster than the removal of the activated product by antithrombin III, an explosive generation of thrombin occurs which can result in thrombus formation. In the present prospective investigation we have therefore made repeated determinations of factor XaI-activity with a newly developed method during and after hip replacement operation to study the possible relation between a sudden decrease in inhibitor activity and the development of postoperative thrombosis. The effect of low dose heparin and dextran on the frequency of postoperative deep vein thrombosis and inhibitor activity was evaluated in separate patient groups.

MATERIAL

Sixty patients, 43 female and 17 male, undergoing total hip reconstruction, were studied. Only patients without known history of previous deep venous thrombosis and with a normal venous outflow capacity of both legs, determined preoperatively with a plethysmographic technique (Bygdeman et al. 1971) were allowed to enter the study. The patients were randomly allotted to three groups (Groups A–C) differentiated by the type of prophylactic antithrombotic treatment used. The mean age and standard deviation in the three groups was: Group A, 70.1 ± 7.2 years; Group B, 66.8 ± 8.3; Group C, 65.7 ± 10.6 years.

TREATMENT

Prophylactic antithrombotic treatment was used in Groups A and B according to the following schema. In Group A 500 ml Macrodex® was given during operation and repeated on the first and fourth postoperative day. Low dose heparin, 5000 IE, was given s.c. preoperatively and repeated every 12 h during the first postoperative week in Group B. In Group C, which served as a control group, no specific prophylactic antithrombotic treatment was given. Routine physiotherapy with early ambulation was used in all the patients.

METHODS

Venous blood samples for XaI determinations were taken on the day before operation, immediately before operation, after anaesthesia, at the start of operation and during operation, 3 hours after operation and on the first postoperative day. Two further samples were taken during the first postoperative week. The blood was collected in citrate and after centrifugation the plasma was frozen at −50°C until analyzed. Blood plasma XaI-activity was determined according to the method of Yin et al. (1977). Test kits, Phadecode® XaI differential assay, were obtained from Pharmacia AB, Uppsala, Sweden. The Phadecode® XaI differential assay consists of a set of two different tests: 1. The Comprehensive Test and 2. The Specific Test. The primary difference between the two methods is that the former utilizes undiluted plasma samples, whereas the latter involves a 200-fold dilution of the plasma sample and the addition of selective polysulfated compound. The Comprehensive Test system measures the overall ability of the plasma to neutralize Xa and is therefore influenced by the presence of any circulation accelerator or antagonist of XaI-activity.

In the Specific Test the high dilution of the plasma sample reduces those effects. The additive substance circumvents the apparent inhibitor action of a naturally occurring plasma component on the XaI – Xa interaction.

The frequency of postoperative deep vein thrombosis was studied by ascending phlebography according to Greitz (1954) and by measurements of venous outflow capacity plethysmographically as described by Bygdeman et al. (1971). Venous outflow capacity was determined on both legs preoperatively and at the end of the second postoperative week. Ascending phlebography was made at the end of the second postoperative week on the operated leg, unless the prior determination of venous outflow capacity indicated a deep vein thrombosis in the opposite leg.

Operative and postoperative blood loss was estimated by swab weighing and measurements of drain volume.

RESULTS

No significant differences in mean values of age, operation time, bleeding volume and number of transfused blood units was found between the three patient groups (Table 1). Postoperative phlebography could be carried out successfully in 16, 17 and 18 of the patients in Groups A, B and C respectively. In the control group, Group C, postoperative phlebography was positive in five patients. One patient developed clinical signs of a pulmonary embolism 10 days after operation,

Table 1. Mean values for age, bleeding volume and number of blood transfusions in the three patient groups

Group	Age	Operation time, min	Operative blood loss, ml	Post operative blood loss, ml	Transfusion during op., units	Transfusion after op., units
A	70.1	101	835	816	2.3	1.9
B	66.8	118	1071	645	2.6	2.2
C	65.7	103	1004	734	2.4	2.1

Table 2. Postoperative thrombo-embolic complications

Group	No. of pat.	Successful phlebography	Post operative thrombosis at phlebography	Pulmonary embolism	Positive plethysmography
A	20	16	4	–	4
B	20	17	8	–	3
C	20	18	5	1	2

which was subsequently confirmed by lung perfusion scintigraphy. The total frequency of postoperative deep vein thrombosis was thus six out of 18 patients, or 33 per cent. In the dextran (Group A) and heparin (Group B) treated groups postoperative deep vein thrombosis was found at phlebography in four and eight patients respectively giving a frequency of postoperative thrombosis of 25 and 47 per cent. A marked decrease in venous outflow capacity to a value below 35 ml × 100^{-1} × min^{-1}, as found in cases with deep venous thrombosis totally obstructing the deep venous outflow from the calf, was found in nine patients postoperatively. In all cases the decrease was found in the operated leg and the presence of a deep venous thrombosis extending up in the femoral vein could be confirmed in eight patients at phlebography. In the remaining patient belonging to the dextran treated group determination of venous outflow capacity was made 1 week after the normal phlebography, indicating that the thrombus had developed during the intervening period. The results are summarized in Table 2. In the control group, but not in the other groups, the patients who developed postoperative deep vein thrombosis were significantly older than the nonthrombotic patients ($P < 0.01$). No difference in operation time and degree of bleeding was found between thrombotic and nonthrombotic patients.

In the control group mean factor XaI-activity was slightly lower during operation and during the postoperative period in those patients developing postoperative thrombosis compared with the activity of the rest of the patients (Figures 1 and 2). The difference was not significant when the specific assay was used. When the comprehensive test was used the difference was probably significant ($P < 0.05$) immediately before operation (sample 2) and on day 5 (sample 9), operation day = day 1. However, there were great individual variations. Factor XaI-activity during operation and during the first postoperative period in eight patients representative of the different patterns observed are presented in Figures 3 and 4. In two patients (Figure 3A and B) a marked decrease in inhibitor activity was observed to 16 per cent of the preoperative level when measured with the comprehensive test system and to 48 and 53 per cent respectively when the specific test system was used. Both these patients developed deep vein thrombosis in the operated leg in calf veins and extending up in the femoral vein. Venous outflow capacity decreased to 20 and 33 ml × 100 ml^{-1} × min^{-1} respectively indicating total obstruction of the deep venous

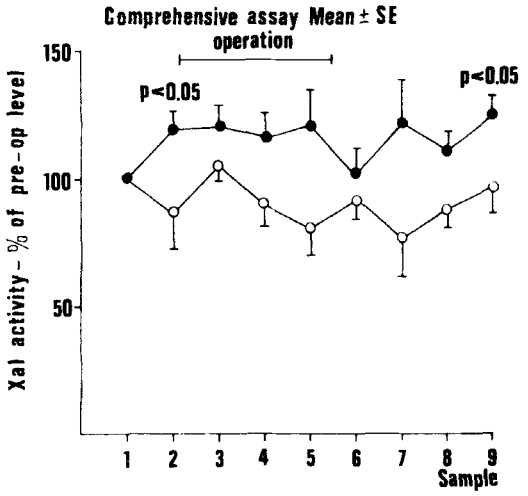

Figure 1. Mean factor Xal-activity measured with the comprehensive test system during and after operation in nonthrombotic patients ●——● and in patients developing postoperative thrombosis ○——○. Operation day = 1.

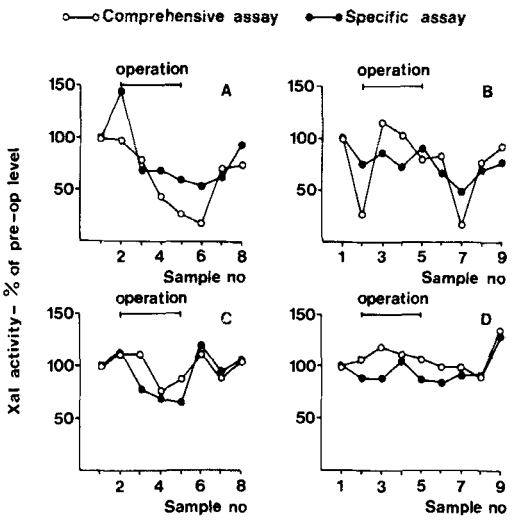

Figure 3. A–D. Factor Xal-activity in per cent of preoperative level in 4 patients developing postoperative deep vein thrombosis.

outflow from the calf. In the nonthrombotic leg no change in outflow capacity was found. In one patient inhibitor activity measured with the specific and comprehensive test system decreased to 66 and 76 per cent, respectively (Figure 3C). In this patient a calf vein thrombosis extending up to but not obstructing the popliteal vein was found. Venous outflow capacity was not decreased. Small deep calf vein thrombosis could be seen in two patients without any significant

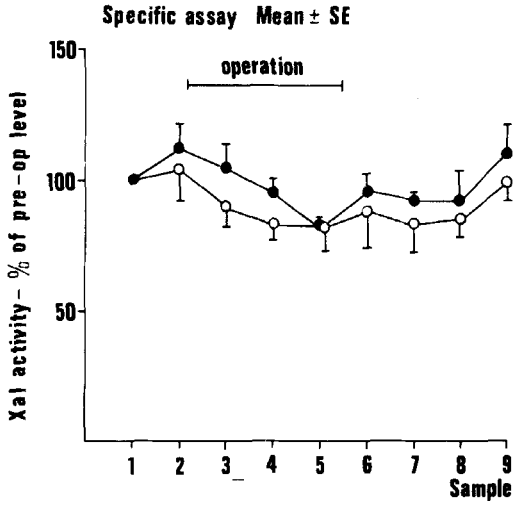

Figure 2. Mean factor Xal-activity measured with the specific test system during and after operation in nonthrombotic patients ●——● and in patients developing postoperative thrombosis ○——○. Operation day = day 1.

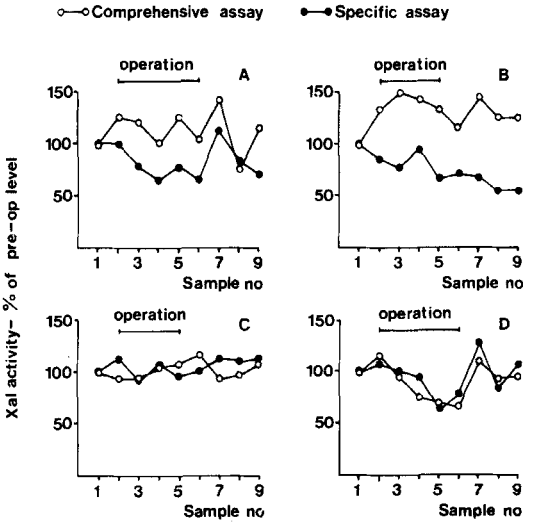

Figure 4. A–D. Different patterns of factor Xal-activity during and after operation in four nonthrombotic patients.

change in inhibitor activity (Figure 3D). In the patient who developed postoperative pulmonary embolism 10 days after operation no change in inhibitor activity was found during the observation period.

In the remaining 12 patients in whom postoperative phlebography could be performed this investigation and venous outflow measurements did not show any signs of deep venous thrombosis. In six of the patients a marked reactive increase of inhibitor activity exceeding 25 per cent in at least two different measurements, when measured with the comprehensive test system, was observed. In two of these patients a decrease of inhibitor activity, measured with the specific test, exceeding 25 per cent was found, indicating inhibitor consumption (Figure 4A and B), while in the remaining patients no significant reduction could be found. In the remaining patients, four showed no change in inhibitor activity measured with the two test systems (Figure 4C). In two patients a decrease of inhibitor activity measured with the comprehensive test was observed, which in one case occurred concomitantly with a similar decrease when the specific test system was used (Figure 4D).

In the group treated with subcutaneous heparin a marked increase in factor XaI-activity was observed with the comprehensive test system (Figure 5). The increase was most obvious in the nonthrombotic patients although the difference

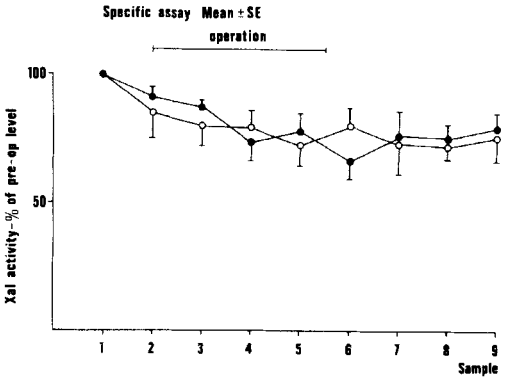

Figure 6. Mean factor XaI-activity measured with the specific assay during and after operation in patients treated with subcutaneous heparin. No postoperative thrombosis ●—●. Patients developing postoperative thrombosis ○—○.

was only significant at the 0.05 level at the end of operation. With the specific test (Figure 6), which measures inhibitor activity independent of heparin, a decrease was observed indicating inhibitor consumption in both thrombotic and nonthrombotic patients. No significant difference in reaction pattern could be observed between the two patient groups.

In the Macrodex treated group the comprehensive test system showed no significant change in FXaI-activity in the nonthrombotic pa-

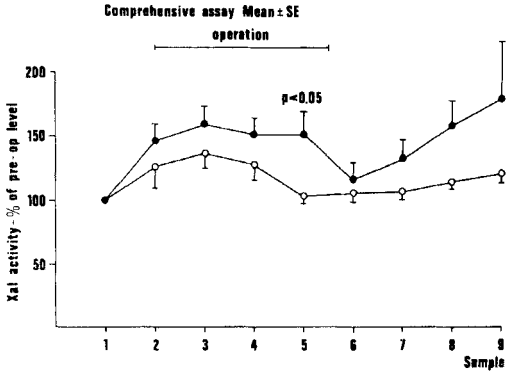

Figure 5. Mean factor XaI-activity measured with the comprehensive assay during and after operation in patients treated with subcutaneous heparin. No postoperative thrombosis ●—●. Patients developing postoperative thrombosis ○—○.

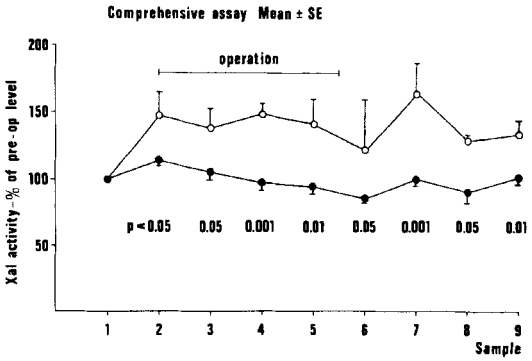

Figure 7. Mean factor XaI-activity measured with the comprehensive assay during and after operation in patients treated with Dextran 70 i.v. No postoperative thrombosis ●—●. Patients developing postoperative thrombosis ○—○.

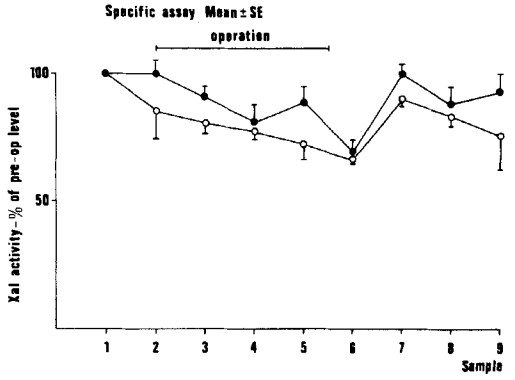

Figure 8. Mean factor XaI-activity measured with the specific assay during and after operation in patients treated with Dextran 70 i.v. No postoperative thrombosis ●—●. Patients developing postoperative thrombosis ○—○.

tients (Figure 7). In the four patients developing postoperative thrombosis an increase in FXaI-activity was found (Figure 7). With the specific assay a decrease in FXaI-activity was observed in both thrombotic and nonthrombotic patients. The difference between the two groups was not significant (Figure 8).

Great individual variations in factor XaI-activity were observed in both the heparin and the dextran 70 treated groups. Eight patients in the heparin group developed postoperative thrombosis. In three of the patients the thrombosis was extensive, occupying calf veins and extending up in the femoral veins. Venous outflow capacity was decreased to 14, 21 and 33 ml × 100 ml^{-1} × min^{-1}. The comprehensive assay showed increased factor XaI-activity secondary to heparin stimulation. A marked decrease in inhibitor activity measured with the specific assay down below 50 per cent was observed in two patients (Figure 9A) and below 70 per cent in one patient. Two patients developed calf vein thrombosis extending up in the popliteal vein causing partial occlusion and a moderate decrease in venous outflow capacity to 45 and 48 ml × 100 ml^{-1} × min^{-1}. In three patients the thrombosis was restricted to calf veins with no influence on venous outflow capacity. In four of the five patients a decrease in inhibitor activity below 75 per cent of preoperative value measured with the specific assay was observed (Figure 9B). In one patient no significant change in inhibitor activity was observed.

In the remaining nine heparin treated patients, in whom phlebography could be performed and no postoperative thrombosis could be demonstrated, six patients showed a significant decrease in factor XaI-activity measured with the specific test system (Figure 9C), while in three patients no significant change was observed (Figure 9D).

In the dextran treated group four patients developed postoperative thrombosis demonstrated by phlebography. Three of the thromboses extended up in the femoral vein causing significant reduction of venous outflow capacity to 23, 35 and 40 ml × 100 ml^{-1} × min^{-1} respectively. In one case the thrombus was restricted to calf veins with no significant reduction of venous outflow capacity when measured with the plethysmographic technique. In all four cases a significant reduction in factor XaI-activity was observed when measured with the specific assay (Figure 10A).

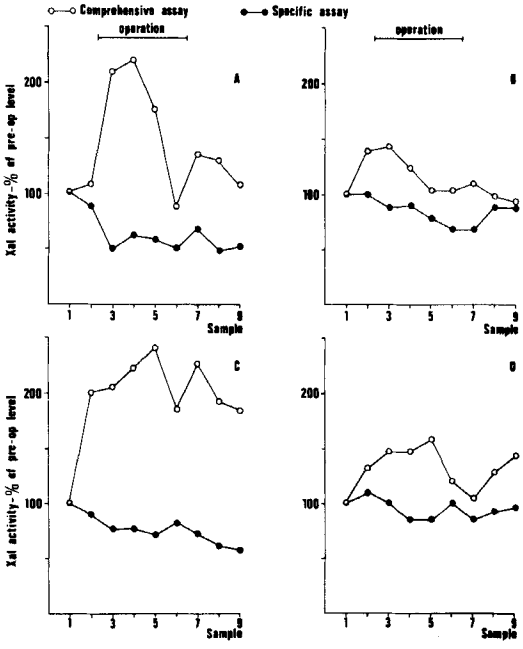

Figure 9. Factor XaI-activity in patients treated with subcutaneous heparin. For details see text.

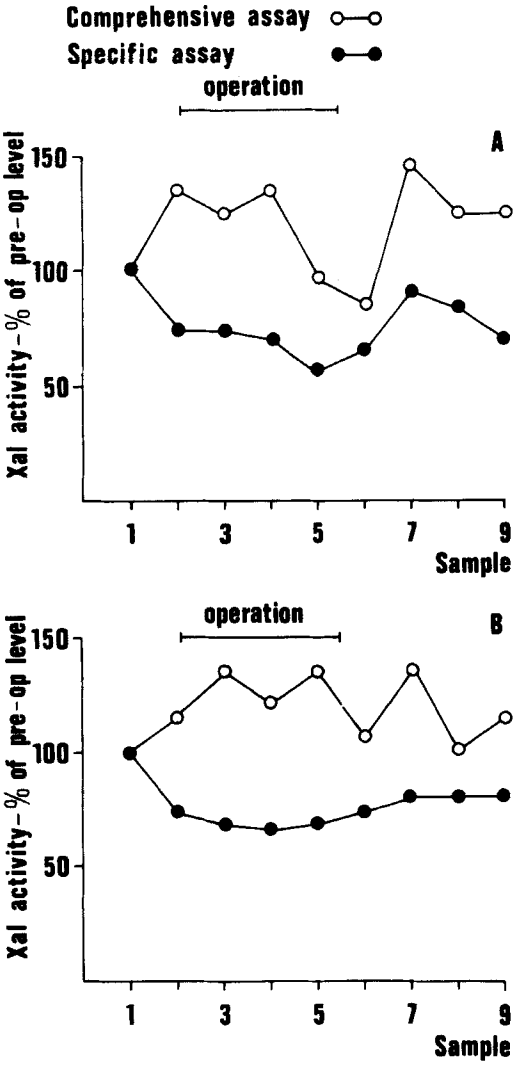

Figure 10. Factor XaI-activity in dextran treated patients. For details see text.

In the remaining 12 patients, in whom phlebography could be performed and no postoperative thrombosis could be demonstrated, seven patients showed a significant decrease in FXaI-activity when measured with the specific test (Figure 10B). In one patient the decrease was combined with a simultaneous decrease in FXaI-activity with the comprehensive test. In three patients a decrease in inhibitor activity was found measured with the comprehensive test without any significant decrease in specific activity.

DISCUSSION

The present investigation is an attempt to study the concept of hypercoagulability during operation and the immediate postoperative period and its relationship to postoperative venous thromboembolism. With the new differential XaI assay, the comprehensive test provides information on the actual overall capacity of the patient's plasma to neutralize activated factor X, while the specific test system measures FXaI-activity independent of circulating stimulators or inhibitors of FXaI-activity. A comparison between the results obtained with the comprehensive and specific assay makes it possible to demonstrate a compensatory mechanism, for instance release of endogenous heparin or to indicate the presence of an antagonist of XaI-activity.

The results obtained in the control group (Group C) show that a marked decrease in inhibitor activity measured with both test systems is a characteristic pattern in patients with extensive thrombus formation. This indicates that the thrombus formation is preceded by a hypercoagulability state with a consumption of FXaI. The simultaneous decrease in FXaI-activity measured with the comprehensive test system is more marked, indicating the possibility that the degree of inhibition of coagulation may be further impaired by an antagonist of FXaI-activity. The decrease in FXaI-activity seems to be related to thrombus size and a calf vein thrombosis can obviously develop without any sustained change in inhibitor activity. It is remarkable that in the patient with postoperative pulmonary embolism no change in FXaI-activity was found. This could be due to the fact that the clinical signs of the embolus did not appear until almost 1 week after the completion of the FXaI-activity measurement.

In a majority of the nonthrombotic patients belonging to the control group an increase in FXaI-activity measured with the comprehensive test system is observed indicating the presence of circulating accelerators of FXaI-activity. This increase can obviously compensate for a decrease in FXaI-concentration as measured with the specific test system (Figure 4A and B) and may be an important mechanism in the prevention of

postoperative deep vein thrombosis. In two patients a decrease in activity measured with the comprehensive test system down to 60 and 65 per cent of preoperative activity respectively was observed, which in one case occurred simultaneously with a decrease in specific activity. A moderate decrease in activity can thus be observed without concomitant thrombus formation. This is not astonishing, since the development of a "hypercoagulable state" is only one of several factors predisposing for thrombosis.

The results obtained are similar to those reported by Gitel et al. (1979) in the respect that a mean decrease in FXaI-activity is found in connection with a total hip replacement operation. However, the results of the present study also indicate that postoperative thrombosis is more likely to occur in those patients who developed a marked decrease in inhibitor activity.

In the heparin treated group a marked increase in FXaI-activity, measured with the comprehensive test system, was found. This increased activity is most likely secondary to an effect of heparin on the inhibitor activity as described by Yin (1974). With the specific test a mean decrease in inhibitor activity was observed, indicating inhibitor consumption in accordance with the assumption that with the specific test it is possible to measure FXaI-activity independent of circulating heparin. In seven of the eight patients developing postoperative thrombosis a significant reduction in inhibitor activity with the specific test was observed. In the nonthrombotic patients a significant decrease in inhibitor activity occurred in six out of nine patients. The thrombus developed in spite of a general increase in inhibitor activity measured with the comprehensive test. In six patients a decrease in activity below 100 per cent at one or more occasions was observed, while in only one patient was an activity level below 75 per cent found. In five of the nonthrombotic patients a similar occasional decrease in activity was recorded. No clear cut difference in reaction of inhibitor activity between patients developing postoperative thrombosis and nonthrombotic patients could be found.

In the dextran treated group a significant reduction in specific inhibitory activity concomitant with an increased activity measured with the comprehensive test was observed in all four patients developing postoperative thrombosis. In the nonthrombotic patients seven showed a decrease in specific inhibitory activity while no general increase in comprehensive inhibitory activity was found. The reason for the difference in reaction pattern when the comprehensive test was used between thrombotic and nonthrombotic patients is unclear.

The hypothesis that a sudden marked decrease in FXaI-activity is associated with an increased risk of thrombus formation is supported by the results obtained in the control group of the present study. In the dextran and heparin treated patients the reaction pattern is much less specific. It is possible, however, that repeated measurements of FXaI-activity during and after operation can be used as an early indication for the need for antithrombotic treatment. It is obvious, however, that FXaI-activity measurements alone cannot be used in the diagnosis of venous thrombosis, since a thrombus can develop without any significant change in XaI-activity.

The frequency of postoperative deep vein thrombosis found in the present study was 25, 47 and 32 per cent in Groups A–C respectively. The difference is not statistically significant. The frequency of thrombosis most likely represents the true incidence of thrombosis, in spite of the fact that only unilateral phlebography was performed, since it has been shown that postoperative thrombosis following hip surgery either is formed in the operated leg or is bilateral (Stevens et al. 1968, Pinto 1970, Bergqvist & Dahlgren 1973). This assumption was also confirmed by the results of postoperative plethysmographic measurements of venous outflow capacity, which in all cases excluded the presence of major thrombosis extending up in the popliteal or femoral veins in the nonoperated leg. The frequency of thrombosis is, however, slightly lower than that found in most studies after elective hip operations (Pinto 1970, Evarts & Feil 1971, Nicolaides et al. 1975, Bergqvist et al. 1976, Sagar et al. 1976). This might be explained by the protocol used, which excluded patients from the study who preoperatively were found to have a decreased venous outflow capacity as a sign of previous deep vein thrombosis and the fact that the

phlebography was carried out as early as the second week after operation (Bergqvist et al. 1976).

ACKNOWLEDGEMENT

Supported by research grants from the Swedish Medical Research Council No. 14x – 1019 and Pharmacia AB to S.B.

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Correspondence to: S. Bygdeman, M.D., Department of Clinical Physiology, St Göran's Hospital, Box 12500, S – 112 81 Stockholm, Sweden.