



FIBRINOLYTIC PARAMETERS IN PATIENTS UNDERGOING TOTAL HIP REPLACEMENT: RELATIONSHIP WITH THE DEVELOPMENT OF ASYMPTOMATIC DEEP VEIN THROMBOSIS AND DIAGNOSTIC USEFULNESS OF VENOUS OCCLUSION

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ABSTRACT

Background and Objective. It has been suggested that impaired fibrinolytic activity contributes to deep vein thrombosis in orthopedic surgery. Studying the fibrinolytic system following venous occlusion has been proposed as a good method of detecting the risk of this postoperative complication. The objective of this work was to verify whether venous occlusion represents a reliable method of detecting an impaired fibrinolytic response after total hip replacement.

Methods. Thirty-two consecutive patients undergoing total hip replacement were studied. Citrated blood samples were taken from each patient the day before surgery and on postoperative days 1, 3, and 7, before and after venous occlusion, in order to evaluate plasma levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1). All patients underwent bilateral phlebography 10 days after surgery.

Results. Seven out of 32 patients (21.9%) developed deep venous thrombosis (DVT) according to the venographic test. After surgery, an increase in t-PA antigen levels was detected both in patients

who developed DVT and in those who did not, with a significant increase on the first and seventh days after surgery only in the non-DVT group. After 10-min venous occlusion, t-PA antigen levels increased at all postoperative recordings in both groups of patients, but most significantly on days 1 and 7 after surgery. PAI-1 antigen plasma levels, when measured before venous occlusion, increased only in non-DVT patients on the seventh postoperative day. After venous occlusion, a difference was found between the two groups only postoperatively on day 7 with regard to PAI-1 levels.

Interpretation and Conclusions. According to our results, no impaired fibrinolytic response was found in DVT patients. In addition, venous stasis seems to give no further information with respect to basal values in the early detection of postoperative thromboembolic complications in orthopedic patients.

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Key words: postoperative deep vein thrombosis, fibrinolysis, tissue plasminogen activator, tissue plasminogen inhibitor, venous occlusion

The incidence of thromboembolic disease (deep vein thrombosis and pulmonary embolism) after major orthopedic surgery is high in spite of current prophylaxis.^{1,3} Evidence has shown that pulmonary embolism is a serious and potentially lethal complication of deep vein thrombosis (DVT).² The pathogenesis of DVT is multifactorial and only partly understood. Several factors are thought to be involved, such as increased blood coagulability, endothelium damage, stasis, and impaired fibrinolytic activity.^{4,5}

Over the years, several studies have investigated the relationship between impaired fibrinolysis and thromboembolic disorders in patients with postoperative DVT.⁶⁻¹³ Even though the fibrinolytic balance is markedly influenced by several factors, two

mechanisms in particular have been investigated in order to evaluate poor fibrinolytic response: defective synthesis and/or release of tissue plasminogen activator (t-PA) and increased levels of the rapid inhibitor of plasminogen activator (PAI-1).^{3,6,7,9-11} Recent evidence indicates that plasma levels of PAI-1 increase postoperatively, and this fibrinolytic inhibitor has been hypothesized to be a major contributor to the fibrinolytic shutdown phenomenon.¹⁴ A recent critical review of these studies has suggested a connection between impaired fibrinolytic activity, measured either preoperatively or postoperatively, and increased risk of postoperative thrombosis.¹⁵ Whether this connection is coincidental or not is still unclear, especially if we consider the inconsistent results of random clinical trials

that used interventions to enhance fibrinolytic activity.¹⁵ Furthermore, only one study evaluated fibrinolytic parameters after applying venous occlusion (VO) in orthopedic patients.⁷ Nevertheless, diagnosis of postoperative DVT was confirmed by venography only in patients who underwent positive I-fibrinogen leg scanning, thus potentially underestimating the incidence of thrombotic events. In this study we investigated a possible connection between impaired fibrinolytic activity and increased risk of thrombosis after total hip replacement. The fibrinolytic response to surgery was evaluated by determining t-PA and PAI-1 antigen plasma levels. Furthermore, we verified whether VO represents a reliable method of detecting an impaired fibrinolytic response after total hip replacement.

Materials and Methods

Patients

Thirty-two consecutive patients (23 women and 9 men; age 51-87 years), undergoing total hip replacement were studied. Informed consent was required for inclusion in the study. All patients were admitted to the hospital one day before surgery and were submitted to specific prophylaxis for DVT with subcutaneous calcium heparin (5,000 I.U. three times daily), starting 12h before the operation. A full-dose regimen of intravenous heparin (30,000 I.U./day) followed by warfarin therapy for at least three months was administered to patients with venographic-proven DVT. Patients were excluded from the study if they had a history of previous DVT, were treated with oral anticoagulant or anti-platelet drugs in the week prior the surgery, had acquired or inherited bleeding disorders, a history of internal bleeding or active peptic ulcer in the past six months, hypersensitivity to heparin, the presence of lupus-like anticoagulant (LAC) or a known deficiency of protein C, protein S and AT-III, or a platelet count less than $100 \times 10^9/L$.

Table 1. Mean plasma levels of t-PA antigen (ng/mL) before (b-V0) and after (a-V0) venous occlusion in patients who developed and those who did not develop DVT after total hip replacement.

days	non-DVT (b-V0)			DVT (a-V0)		
	mean±DS	n	p	mean±DS	n	p
-1	6.8±4.2	22	—	5.5±2.6	7	—
+1	9.8±4.2	22	0.004	8.9±4.2	7	n.s.
+3	8.5±3.9	16	n.s.	7.1±3.1	7	n.s.
+7	9.9±5.4	20	0.02	7.4±4.7	7	n.s.

days	non-DVT (b-V0)			DVT (a-V0)		
	mean±DS	n	p	mean±DS	n	p
-1	9.1±4.5°	22	—	7.9±2.9*	7	—
+1	14.7±6.4°	23	0.002	15.9±4.2*	7	0.02
+3	12.9±4.9°	19	n.s.	10.6±4.6	7	n.s.
+7	16.2±6.3°	17	0.001	12.4±6.2*	6	0.03

n = number of observations; -1 = 1 day before surgery; +1, +3, +7 = 1, 3, 7 days after surgery; p = significance of changes within groups (DVT and non-DVT) as compared to preoperative values. The statistical significance of differences between b-V0 and a-V0 levels within groups is indicated: °p=0.001; *p=0.05.

Blood samples

Venous blood samples for the fibrinolytic tests were collected from each patient the day before surgery and on postoperative days 1, 3, and 7 between 8:00 a.m. and 10:00 a.m. after overnight fasting and a 15-min rest in the supine position. VO was performed for 10 min by applying a sphygmomanometer cuff inflated to a pressure midway between the systolic and the diastolic values. Nine volumes of blood were mixed with one volume of 0.129 M trisodium citrate. After centrifugation ($3,000 \times g$ for 20 min) the samples were stored at $-80^\circ C$ for less than two months before testing.

Diagnostic procedures

Bilateral ascending phlebography was performed on the 10th postoperative day, using the method of Rabinov and Paulin.¹⁶ The criterion for acute DVT was the presence of a complete intraluminal filling defect in at least two projections. t-PA antigen was measured manually with an enzyme-linked immunoassay (TintElize t-PA, Biopool, Umea, Sweden) which utilizes the double antibody principle to quantify human single-chain and two-chain tissue plasminogen activator antigens. PAI-1 antigen endothelial type was also measured manually with an enzyme-linked immunoassay (TintElize PAI-1, Biopool, Umea, Sweden) utilizing a polyclonal antibody against PAI-1 that recognizes the latent, the free, and the complexed form to about the same extent. Both t-PA and PAI-1 were dosed by technicians unaware of the patient's clinical condition or the results of venography. All assays were performed in duplicate and the values reported represent the average of the two assays.

Statistical analysis

Since fibrinolytic variables were not normally distributed, non-parametric tests were employed. The two-tailed Mann-Whitney U test was used to test for differences between patients who developed thromboembolism and those who did not (DVT and non-DVT patients, respectively). The significance of day-to-day variations within groups before and after VO was established by Friedman's test. The Wilcoxon signed-rank test was used to define which data couple was responsible for significance. The Wilcoxon signed-rank test was also utilized for comparing t-PA and PAI-1 levels within groups before and after VO. A p-value less than 0.05 was regarded as significant.

Results

DVT was detected by ascending phlebography in 7 out of 32 patients (21.9%). All DVT were asymptomatic and none of the patients developed signs or symptoms of pulmonary embolism.

t-PA antigen levels before VO

There was no difference between DVT and non-DVT patients at any time. t-PA antigen levels were always higher in both groups, but only significantly so with respect to the preoperative values in non-DVT patients on the first and seventh postoperative days (Table 1).

t-PA antigen levels after VO

There was no difference between DVT and non-DVT patients at any time. t-PA antigen levels were higher than preoperative values in both groups at all postoperative recordings, but only significantly so on the first and seventh postoperative days. The mean values of t-PA antigen levels were increased after VO in both groups at each point in time compared to the recordings before VO, with the exception of day 3 after surgery in DVT patients (Table 1).

PAI-1 antigen levels before VO

Mean PAI-1 plasma levels before VO were not significantly different between the two study groups at any point in time. PAI-1 antigen levels were only significantly higher one week after surgery in patients who did not develop DVT (Table 2).

PAI-1 antigen levels after VO

The mean values of PAI-1 antigen were significantly higher than before VO at all recordings only in non-DVT patients. There was a difference between DVT and non-DVT patients only postoperatively at day 7, with higher PAI-1 levels occurring in non-DVT patients. However, no significant increase after surgery was detected in either group when compared to preoperative values (Table 2).

Discussion

Our results do not enable us to conclude that impaired fibrinolysis contributes to the pathogenesis of thromboembolic complications after major orthopedic surgery. In fact, an increase in basal t-PA antigen levels was detected in both DVT and non-DVT patients after surgery, although it was significant only in the non-DVT group on the first and seventh postoperative days. On the other hand, after 10-min venous occlusion we observed a significant increase of t-PA antigen plasma levels in both DVT and non-DVT patients on the first and seventh postoperative days as compared to baseline values. Patients who developed DVT showed a less marked increase after VO, but this could be attributed to the lower number of subjects with respect to the

non-DVT group. Thus, 10-min VO seems to provide no further information on the early detection of thromboembolic risk in orthopedic patients, despite the findings of previous studies that proposed evaluation of t-PA antigen levels after an appropriate stimulus (venous stasis, desmopressin infusion, strenuous exercise, etc.) as a reliable way of assessing the fibrinolytic capacity of endothelial cells.¹⁷ As suggested by Keber *et al.*,¹⁸ the endothelium is probably not stimulated by VO and stasis could be responsible for increased t-PA levels through a progressive accumulation of basal t-PA rather than through induction of its secretion. Whether values recorded before stasis are more suitable than those reported after stasis in determining the two groups of patients should be confirmed on a larger number of observations.

With regard to PAI-1 levels, only one study⁷ investigated the fibrinolytic system in surgical patients under an appropriate stimulus such as VO. The present study cannot confirm findings in previous reports that patients who develop DVT after hip surgery have significantly higher levels of PAI-1 antigen and/or activity before and/or after surgery than who do not develop DVT.^{3,7,8,10} In fact, according to our findings PAI-1 levels measured before stasis increased significantly with respect to preoperative values only in non-DVT patients on the seventh postoperative day. On the other hand, after venous occlusion we observed a significant difference between the two study groups only one week postoperatively, with higher levels of PAI-1 being found in patients who did not develop DVT. A significant increase in PAI-1 levels with respect to baseline values was detected after stasis only in the non-DVT group at all recordings. Finally, since PAI-1 has been shown to be an acute-phase reactant to tissue injury,^{19,20} this parameter probably has a low sensitivity and specificity for diagnosing DVT after arthroplasty.

Methodological differences among the assays used for detection of PAI-1 and t-PA, differences in prophylactic regimens and surgical treatment, as well as in the screening methods employed for DVT render direct comparisons between studies difficult and inconclusive.²¹ Genetic susceptibility to venous thrombosis may represent an additional confounding factor.²² Thus, although impaired fibrinolytic activity has been hypothesized to contribute significantly to the pathogenesis of postoperative thrombosis, there have been few randomized clinical trials which used interventions to enhance fibrinolytic activity and they have yielded inconsistent results. In conclusion, according to our study the relationship between impaired fibrinolysis and DVT after total hip replacement is still unclear and 10-min VO does not seem to be a reliable procedure for assessing fibrinolytic capacity in orthopedic patients.

Table 2. Mean plasma levels of PAI-1 antigen (ng/mL) before (b-V0) and after (a-V0) venous occlusion in patients who developed and those who did not develop DVT after total hip replacement.

days	non-DVT (b-V0)			DVT (a-V0)		
	mean±DS	n	p	mean±DS	n	p
-1	32.0±13.9	18	—	40.1±21.4	7	—
+1	36.6±10.5	21	n.s.	34.0±12.7	7	n.s.
+3	30.5±10.8	16	n.s.	31.9±9.4	6	n.s.
+7	48.8±14.0	19	0.002	38.9±11.5	7	n.s.

days	non-DVT (b-V0)			DVT (a-V0)		
	mean±DS	n	p	mean±DS	n	p
-1	41.5±15.4°	20	—	43.6±24.4	7	—
+1	41.7±13.7^	20	n.s.	34.8±12.8	7	n.s.
+3	35.9±18.0*	19	n.s.	39.0±12.2	7	n.s.
+7	55.3±11.0*	15	n.s.	44.2±13.5	7	n.s.

n = number of observations; -1 = 1 day before surgery; +1, +3, +7 = 1, 3, 7 days after surgery; p = significance of changes within groups (DVT and non-DVT) as compared to preoperative values. The statistical significance of differences between b-V0 and a-V0 levels within groups is indicated: °p=0.001; *p=0.05; ^p=0.01.

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