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Value of Thrombin-Antithrombin III Complexes in Major Orthopedic Surgery: Relation to the Onset of Venous Thromboembolism

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Summary: This study evaluated (a) the possible changes of plasma levels of thrombin-antithrombin III complexes during hospitalization to predict venous thromboembolism in patients undergoing elective total hip replacement and (b) the sensitivity and specificity of thrombin-antithrombin III complexes in the late incidence of deep vein thrombosis when these patients are discharged from the hospital. In 50 consecutive patients (18 men, mean age = 63 ± 8 years) a venous blood sample was obtained from each patient before surgery and postsurgery on days 5 ± 2, 9 ± 2, and 45 to evaluate the thrombin-antithrombin III complexes by the enzyme-linked immunosorbent assay as a part of a larger surveillance program. Six of 50 patients developed deep vein thrombosis, diagnosed by phlebography on the 45th day postsurgery. From the day before until the ninth day after surgery, mean values of the thrombin-antithrombin III complexes increased to a greater extent in patients with deep vein thrombosis than in those without, although the differences were not significant (from 14.8 ± 11.2 ng/mL to 36.2 ± 19.1 ng/mL in the former group and from 13.6 ± 3.3 ng/mL to 22.4 ± 5.1 ng/mL in the latter, p = NS). On the 45th day after surgery the mean value of the thrombin-antithrombin III complexes reduced less in patients with deep vein thrombosis (up to 9.9 ± 1.9 ng/mL and to 25.2 ± 17.2 ng/mL, respectively, p = NS). In addition, thrombin-antithrombin III complexes remained over the level reached on the fifth day only in the patients who developed deep vein thrombosis. On the 45th day after surgery, thrombin-antithrombin III complexes exhibited a sensitivity of 17%, a specificity of 86%, and an accuracy of 78% in differentiating the presence and absence of deep vein thrombosis as compared with phlebography. We conclude that after total hip replacement (a) serial measurement of the thrombin-antithrombin III complexes does not appear helpful in predicting venous thromboembolism during hospitalization, and (b) measurement of thrombin-antithrombin III complexes has a low diagnostic accuracy in diagnosing delayed deep vein thrombosis. However, the greater and persistent increase of thrombin-antithrombin III complexes level in patients who developed deep vein thrombosis may deserve further investigations. **Key Words:** Hip replacement—Thrombin-antithrombin III complexes—Deep vein thrombosis—Pulmonary embolism—Phlebography—Plethysmography impedance.

Venous thromboembolism (VTE) occurs frequently in the postoperative period (1,2) and more frequently after hospital discharge (3–7). Although angiography and phlebography remain the criterion standard techniques to diagnose pulmonary embolism (PE) and deep vein thrombosis (DVT), many attempts have been made to find laboratory tests that could help with the diagnosis of these pathologies (8–19).

In particular, D-dimer and thrombin-antithrombin III (TAT) complexes determinations were evaluated. At present, it is accepted that the D-dimer test can be the most useful test in excluding VTE because of its high sensitivity (about 95%) (8,17), while the specificity is relatively low. Therefore, a positive D-dimer test needs confirmation by other more specific diagnostic techniques (1). The TAT complexes in screening for VTE sensitivity is reported to be from 72% to 100% and the specificity from 25% to 100% (9–13,19). However, changes in the D-dimer and TAT complexes might be more useful in predicting VTE during the postoperative period of high risk patients where symptoms and signs may be absent or totally nonspecific. However, they may be of help later when patients are back home and the risk of VTE remains high (5–7).

This study evaluated (a) the possible changes of plasma levels of TAT complexes during hospitalization to predict VTE in patients undergoing elective total hip replacement (THR), and (b) the sensitivity and specificity of TAT complexes in delayed DVT, when these patients are discharged from the hospital.

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PATIENTS AND METHODS

During 1 year, 61 consecutive patients (20 men and 41 women, mean age = 66 ± 10 years) were admitted to the Orthopedic Department of the University of Pisa for elective THR and were included in this study. The study was approved by the Institutional Ethical Committee on human research. On admission, each patient gave informed consent and was interviewed to obtain a recent and past history with particular attention paid to predisposing conditions for VTE and comorbid pathologies. After physical examination, each patient had a Computerized Impedance Plethysmography (CIP) using an automatic device CIP 8/32 (Akern, Florence, Italy); if the result was abnormal the patient was excluded from the study.

Total hip replacement was performed with a posterolateral approach using spinal anesthesia. Standard postoperative mobilization consisted of sitting out of bed on the first or second postoperative day, standing nonweight bearing on the third day, and walking with partial weight bearing as tolerated with a walker or with the use of crutches later on. All patients were able to achieve the postoperative mobilization program. Patients had prophylaxis with subcutaneous heparin (15,000 IU/daily) from the day before surgery until the day of hospital discharge.

To depict early the occurrence of DVT or PE during the hospitalization period, a surveillance program was conducted by performing a (a) physical examination everyday during the hospitalization period; (b) CIP on postoperative days 5 ± 2 and 9 ± 2 and on the day before discharge; and (c) blood gas analysis to evaluate PaO_2, $PaCO_2$, and pH, on the fourth and seventh postoperative day. If CIP became positive during the surveillance period, contrast phlebography was performed within 24 hours on the positive limb to confirm or rule out the presence of DVT. If cardiopulmonary symptoms and/or blood gas analysis data raised the suspicion of PE, perfusion lung scan and/or selective pulmonary angiography were promptly performed.

On the day before surgery and on the 5th, 9th, and 45th day after surgery a citrated venous blood sample (9 parts of blood and 1 part of 32 g/L trisodium citrate dihydrate solution) was obtained to evaluate TAT complexes. Blood was immediately centrifuged at 3,000 rpm for 15 minutes and plasma was separated into a test tube and frozen at –80°C until assessment. The antigenic levels of the TAT complexes were evaluated by an enzyme-linked immunosorbent assay (ELISA) using a commercial kit ("Enzignost-TAT," Behringwerke, Marburg, Deutchland) in accordance with the manufacture's instructions and following a described technique (20).

FOLLOW-UP

All patients were followed for 30 days after discharge. Family physicians were asked to send patients back to our hospital if signs or symptoms of DVT or PE occurred. Once again, in patients with suspected DVT or PE, CIP was repeated in every instance, and phebography or perfusion lung scan and/or pulmonary arteriography were promptly performed. All patients were recalled on the 45th day after THR to perform CIP on both limbs and phlebography on the operated limb. Phlebography was interpreted separately by two expert radiologists, who not only determined the presence or absence of DVT, but also the putative age of thrombi; to this end a thrombus was considered as recent when it had a consistent slightly opalescent appearance with a thin layer of contrast surrounding it ("railroad track").

STATISTICAL ANALYSIS

Quantitative variables were presented as mean ± SD or mean ± standard error (SE) when it was more appropriate; qualitative variables as absolute and relative (%) frequencies. Patients were divided into two groups, with and without DVT and the mean values of TAT were compared by unpaired t test. All statistical tests were two-sided with a value of $p < .01$ considered to be significant. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of TAT in diagnosing DVT were calculated using an upper limit of normality of 20 ng/mL; this value was equal to the mean value plus 2 SD of values obtained before surgery in patients who were scheduled for elective THR in our series.

RESULTS

Among 61 admitted patients, 3 were excluded from the study because preoperative CIP was abnormal, and 8 patients were lost to follow-up because they lived far from our hospital. Therefore, the number of patients eventually studied was 50 (18 men, mean age 64 ± 10, range = 30–83 years). No patient had symptoms, signs, or blood gas modifications suggesting VTE or a positive CIP during hospitalization. On the 45th day after surgery, phlebography performed on the operated limb showed DVT in 6 (12%) of 50 patients, and all thrombi were considered recent because of their radiological appearance. Proximal DVT was documented in 4 (8%) and calf DVT in 2 (4%). Of these, one patient showed an abnormal CIP (17%).

Predisposing conditions for VTE and comorbid pathologies recorded before surgery are summarized in Table 1. No significant difference was found between patients with DVT and those without DVT (p = NS).

Before surgery, mean values of TAT complexes were

TABLE 1. *Predisposing conditions for VTE and comorbid pathologies observed in 50 patients scheduled for THR*

Predisposing conditions and comorbid pathologies	All patients (n = 50)		Patients with DVT (n = 6)		Patients without DVT (n = 44)		
	n	(%)	n	(%)	n	(%)	*p*
Obesity*	24	(48.0)	5	(83.3)	18	(40.9)	NS
Smoke	7	(14.0)	1	(16.6)	6	(13.6)	NS
Heart disease	3	(6.0)	1	(16.6)	2	(4.5)	NS
COPD	3	(6.0)	1	(16.6)	2	(4.5)	NS
Malignant neoplasm	1	(2.0)	0	(0)	1	(2.2)	NS
Previous PE	0	(0)	0	(0)	0	(0)	NS
Previous DVT	5	(10.0)	1	(16.6)	4	(9.0)	NS
Rheumatoid arthritis	6	(12.0)	0	(0)	6	(13.6)	NS

*Calculated by Body Mass Index (BMI)

VTE, venous thromboembolism; THR, total hip replacement; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

similar in patients who developed DVT and in patients who did not (14.8 ± 11.2 ng/mL and 13.6 ± 3.3 ng/mL, respectively). From the day before until the fifth and ninth days after surgery, mean values of TAT complexes increased to a greater extent in patients with DVT than in patients without DVT, although differences were not statistically significant (from 14.8 ± 11.2 ng/mL to 23.6 ± 12.6 ng/mL and to 36.2 ± 19.1 ng/mL, respectively, in the former group and from 13.6 ± 3.3 ng/mL to 14.7 ± 2.9 ng/mL and to 22.4 ± 5.1 ng/mL, respectively, in the latter group; p = NS for all comparisons [Fig. 1]). Since the ninth day after surgery, the mean values of TAT complexes reduced in both groups of patients. However the extent of reduction was smaller in patients with DVT (from 36.2 ± 19.1 ng/mL to 25.2 ± 17.2 ng/mL in the former group and from 22.4 ± 5.1 ng/mL to 9.9 ± 1.9 ng/mL in the latter group; p = NS; Fig. 1). Interestingly, only in the patients who developed DVT did the values remain over the level reached on the fifth day after surgery (Fig. 1).

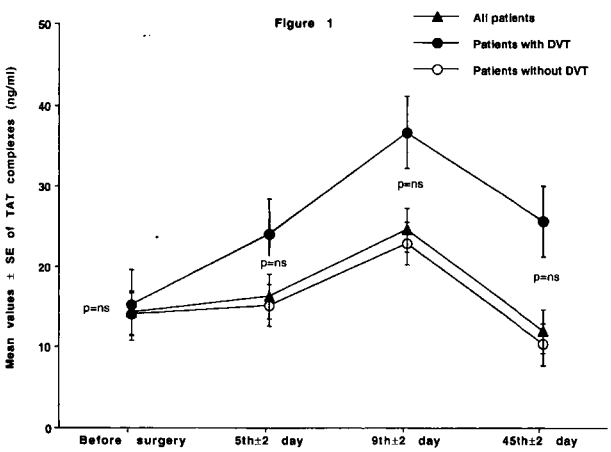

FIG. 1. Changes of mean levels of TAT complexes in patients with and without DVT from the day before surgery until the 45th day after THR.

As to the diagnosis of delayed DVT, values of TAT complexes measured on the 45th day after surgery exhibited a sensitivity of 17%, a specificity of 86%, and an accuracy of 78% in depicting DVT as compared with phlebography (Table 2).

DISCUSSION

Major orthopedic surgery is a well known risk factor for VTE because of the large tissue damage caused by operation and the great intravascular fibrin formation. The risk is present during hospitalization and persists after discharge from the hospital (3–7). During hospitalization the suspicion of VTE can hardly be raised on the basis of symptoms and/or blood gas modifications, since they are absent or difficult to interpret. Therefore, a reliable and simple laboratory test to predict VTE in such patients would be helpful. Until today, the role of the D-dimer and TAT complexes in excluding VTE in patients with clinical suspicion or to reinforce the diagnostic accuracy of other techniques has been evaluated (8–19). However, since TAT complexes represent a specific marker of ongoing thrombin generation we investigated their changes during the entire hospitalization period to raise the suspicion of VTE after THR earlier.

In our study, TAT complexes increased from the day before surgery until the ninth day after THR in all patients. As expected, the low dose of unfractioned heparin (15,000 IU/daily) that the patients received as prophylaxis was ineffective in avoiding the increase of TAT complexes (21–22). Nevertheless, on the fifth and ninth days, the mean levels of TAT complexes were higher in patients who developed DVT in respect to the remainders. These differences were not statistically significant, perhaps because of the small sample size. Therefore, such a result, though interesting, does not allow a definitive judgment about the use of TAT complexes to determine the presence of VTE during the hospitalization period. One could argue that high levels of TAT complexes could be due to pathologies different from VTE, such as malignant disease (one case in our series) or rheumatoid

TABLE 2. *Performance of TAT complexes, measured 45 days after THR, to diagnose delayed DVT as compared with phlebography*

	DVT present	DVT absent
TAT > 20 ng/mL	1 (TP)	6 (FP)
TAT < 20 ng/mL	5 (FN)	38 (TN)
Sensitivity = TP/TP + FN = 17%		
Specificity = TN/FP + TN = 86%		
Positive Predictive Value = TP/TP + FP = 14%		
Negative Predictive Value = TN/TN + FN = 88%		
Accuracy = TP + TN/TP + TN + FP + FN = 78%		

TAT, thrombin-antithrombin III; DVT, deep vein thrombosis; TP, true positive; FP, false positive; TN, true negative; FN, false negative.

arthritis (six cases). However, in our series, both these pathologies did affect patients who had no phlebographic evidence of DVT and whose levels of TAT complexes before surgery were similar to those of the remaining patients. On the 45th day after surgery, TAT complexes returned to the same levels observed before surgery in patients without DVT, while in patients who developed DVT the TAT complexes remained higher than on the fifth day after surgery. Such a persistence of high levels of TAT complexes is clear and potentially useful in selecting patients at high risk for VTE. However, the lack of a statistically significant difference between the two groups of patients does not allow, once again, definitive conclusions.

In our study, the rate of delayed DVT is high (12%), but similar to that reported by others (4,6,7). Since phlebography was performed on postsurgical day 45, we could evaluate the potential role of TAT complexes in the diagnosis of delayed DVT. The result is that TAT complexes do not exhibit a good sensitivity and specificity for the diagnosis of delayed DVT, despite the use as a cutoff of an upper-normal limit of 20 ng/mL. In fact, the sensitivity was 17%, indicating that the great majority of patients with DVT would pass undiagnosed if such a test was used for diagnosis. One could argue that we measured TAT complexes on a fixed day (postsurgery day 45) possibly far from the onset of DVT, when the TAT complexes could be normalized because of their short half-life (23). Although this may be possible indeed, all DVTs were considered of recent onset by two radiologists according to their radiological appearance.

We may conclude that, at present, serial measurement of TAT complexes does not appear to indicate the early suspicion of VTE during hospitalization, nor to diagnose delayed DVT in patients who have undergone THR. However, the high and persistent level of TAT complexes observed in patients who develop DVT far from hip surgery deserve to be controlled in a multicenter trial enrolling a greater number of patients.

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