

PREOPERATIVE PLASMA LEVELS OF PROTHROMBIN FRAGMENT 1 + 2 CORRELATE WITH THE RISK OF VENOUS THROMBOSIS AFTER ELECTIVE HIP REPLACEMENT

A. CORRADI¹, F. LAZZARO¹, E. COFRANCESCO³, M. CORTELLARO³, F. RAVASI², F. BERTOCCHI³

Better preoperative identification of those patients at high risk of developing a deep vein thrombosis (DVT) after hip surgery could reduce the incidence of this postoperative complication, which still occurs despite prophylaxis. One hundred fifty-nine patients undergoing elective total hip replacement and given anticoagulant prophylaxis, were investigated, looking for the presence of a hypercoagulable state, that represents one element of Virchow's triad predisposing to DVT. Plasma levels of three markers of coagulation activation, namely prothrombin fragment 1 + 2 (F1 + 2), thrombin-antithrombin III complexes (TAT) and D-dimer were measured using ELISA procedures and were correlated with the results of the postoperative phlebography. A high correlation ($p < 0.001$) between the preoperative plasma levels of F1 + 2 and the risk of postoperative venous thromboembolism was detected. The performance of TAT and D-dimer levels in predicting DVT was lower.

These findings support the hypothesis that preoperative measurement of coagulation activation markers might be useful in predicting DVT following a total hip replacement.

Keywords : deep vein thrombosis ; hip surgery ; coagulation markers.

Mots-clés : thrombose veineuse profonde ; chirurgie de la hanche ; marqueurs de la coagulation.

INTRODUCTION

Venous thromboembolism is the most common and potentially the most serious immediate postoperative complication of hip surgery.

The incidence of deep vein thrombosis (DVT) after elective hip replacement has been reported to be 45 to 70%, with a 1 to 20% occurrence rate

of pulmonary emboli, and a fatal outcome in up to 6.7% of these cases (3, 5, 9). Such occurrence is recognized to be the culmination of thromboembolic disease, so the prevention of this postsurgical complication has become an integral part of the management of the patient undergoing total hip replacement.

Despite pharmacological prophylaxis, DVT still occurs in a relatively large number of patients, up to 56% (2, 7, 10, 12). It would be helpful if those patients at high risk for DVT could be identified preoperatively to give them a more effective prophylactic regimen.

The aim of this study was to correlate the preoperative plasma levels of three coagulation markers, prothrombin fragment 1 + 2 (F 1 + 2), thrombin-antithrombin III complexes (TAT) and D-dimer, with DVT occurrence after elective total hip replacement.

MATERIALS AND METHODS

The present study was a satellite protocol of a double-blind, multicenter study on the efficacy of recombinant hirudin in comparison with unfractionated heparin in 159 patients undergoing elective hip replacement.

The characteristics of the patients entered in the present protocol are summarized in table I.

¹ 1st and ² 4th Orthopaedic Department and ³ Institute of Internal Medicine. University of Milano, Italy.

Correspondence and reprints : F. Lazzaro, Prima Clinica Ortopedica dell'Università di Milano. Via G. Pini, 3. I-20122 Milano, Italy.

Table I. — Demographic data of the 159 patients examined

Patients' characteristics		
total number of patients	159	
males	41	(25.8%)
females	118	(74.2%)
mean age (yrs) (range)	64.1	(31-84)
mean weight (kg) (range)	66.8	(40-96)
mean height (cm) (range)	162	(148-183)
Diagnosis		
Osteoarthritis	54	(6.9%)
rheumatoid arthritis	3	(1.9%)
osteonecrosis	2	(1.3%)
Concomitant pathologies		
diabetes mellitus	12	(7.5%)
varicose veins	27	(17%)
cardiac diseases	3	(1.9%)

None of the patients had evident comorbid conditions that could independently affect F1 + 2, TAT and D-dimer levels.

The patients randomly assigned to the first group were administered subcutaneously with 10, 15, or 20 mg of recombinant hirudin (TMRevasc, Ciba Geigy Ltd, Switzerland) twice daily. The patients randomly assigned to the second group were treated with 5000 IU of unfractionated heparin three times daily subcutaneously. All treatments were started just before surgery and continued for 8 to 11 days.

The incidence of DVT was evaluated by bilateral ascending phlebography at the end of the prophylactic treatment (or earlier if clinical symptoms occurred). Pulmonary embolism was confirmed by ventilation/perfusion scan or pulmonary angiogram.

Laboratory tests were performed by a single technician who was unaware of the results of phlebography, with an enzyme immunoassay sandwich test (D-dimer dosed by Dimertest EIA kit, Agen, F 1 + 2 and TAT by Enzygnost F 1 + 2 and Enzygnost TAT micro, Behring).

To assess the relation of the preoperative value of any coagulation factor with the phlebographic findings, the values of coagulation variables were grouped according to the distribution third to which they belonged. The statistical analysis computed the chi-square values and the corresponding values of probability. We considered the difference as significant with $p < 0.05$.

Performances of preoperative F1 + 2, TAT complexes and D-dimer plasma levels in predicting postoperative deep vein thrombosis, namely sensitivity, specificity,

positive and negative predictive values, were also calculated using the 1 and 2 cutoff points set at the lower limit of the second and third third of distribution of the plasma levels of the coagulation markers respectively.

RESULTS

We had to exclude from the final analysis the data from 38 of the 159 patients enrolled in the study (23.9%) because they refused to undergo phlebography at the end of treatment or because the examination was not bilaterally executed or was unilateral and negative (12 cases). Twenty-six phlebograms were also judged qualitatively inadequate.

Forty-four of the remaining 121 patients (36.4%) had a phlebogram positive for DVT. The filling defects were proximal in 19 cases (15.7%) and distal, in tibiofibular or muscular veins, in 25 cases (20.6%). Neither episodes of confirmed pulmonary embolism nor deaths were observed (table II).

Table II. — Detailed results of phlebographic evaluation

Patients scheduled	159
Phlebography not evaluated	38 (23.9%)
withdrawn consent or	
unilaterally performed	12 (31.6%)
inadequate quality	26 (68.4%)
Phlebography evaluated	121
positive	44 (36.4%)
proximal filling defects	19 (15.7%)
distal filling defects	25 (20.7%)
negative	77 (63.6%)

Thrombosis incidence for thirds of distribution of F1 + 2, TAT and D-dimer plasma levels was 18.8% in the low (0.75 to 1.33 nM) vs 65.7% in the high third of distribution (1.77 to 3.47 nM) of F1 + 2 ($p = 0.001$), 27.3% in the low (2.00 to 2.50 g/l) vs 57% in the high third (5.10 to 61.00 g/l) of TAT ($p = 0.042$) and 29.4% in the low (39 to 59 g/l) vs 57.1% in the high third (129 to 651 g/l) of D-dimer ($p = 0.051$) (table III).

These results refer to a total of 121 cases, but for each of the three variables considered there are missing values so that the total number of

Table III. — Thrombosis incidence for third of distribution of the coagulation markers

	lower third	higher third	p-value
F1+2	18.8%	65.7%	0.001
TAT	27.3%	57%	0.042
D-dimer	29.4%	57.1%	0.051

Note: Lower and higher third of distribution of the coagulation marker plasma levels: F1+2 = 0.75 to 1.33 nM and 1.77 to 3.4 nM; TAT = 2.00 to 2.50 µg/l and 5.10 to 61.00 µg/l; D-dimer = 39 to 59 µg/l and 129 to 651 µg/l.

values is 102 for D-dimer and 101 for F1 + 2 and TAT.

An increased incidence of DVT with increasing values of coagulation activation markers was observed, with no difference between proximal and distal thrombosis.

The sensitivity, specificity and positive and negative values calculated with the lower cutoff point of the second and third thirds of distribution of the three variables are presented in table IV.

DISCUSSION

It is widely accepted that lower limb orthopedic surgery carries a relatively high risk for a thromboembolic event. Surgical maneuvers, leading to vessel stretching or kinking, are potentially deleterious for the vascular endothelium, where an exposition of collagenic and other procoagulant molecules might occur. Also the bone damage due to reamers may trigger the availability of throm-

boplastic substances that lead to intravascular coagulation. Another risk factor for DVT is represented by venous stasis secondary to bed rest and immobilization.

Even though the presence of a hypercoagulable state often associated with the aforementioned two other elements of Virchow's triad (vascular trauma and intravenous stasis) could play an important role in predisposing to DVT after hip replacement, definitive results about a relationship between development of DVT and coagulation activation markers are not yet available (1, 8, 11).

Hoek *et al.* (6), in a series of 196 consecutive patients who underwent elective total hip surgery, found that TAT plasma level was significantly higher in patients developing DVT, but statistical analysis showed that this parameter had no clinical utility in predicting postoperative deep vein thrombosis.

On the contrary Ginsberg *et al.* (4), in their analysis of 98 subjects undergoing a total hip or knee replacement, found a positive correlation between TAT levels and a calf or proximal thrombosis. Using cut-off points of 3.5 and 5.5 micrograms/l for the TAT level, they also categorized patients as high, intermediate and low risk.

Our data suggested that there was a high correlation between the preoperative plasma levels of F1 + 2 and the risk of DVT after total hip replacement. The performance of TAT and D-dimer levels in predicting DVT was lower.

Based on these results it is possible to calculate the relative risk for DVT. For example a preoperative F1 + 2 concentration of less than 1.34 nM

Table IV. — Performances of preoperative F1 + 2, TAT complexes and D-dimer plasma levels in predicting postoperative deep vein thrombosis. 1 and 2 cutoff points are set at the lower limit of the second and third third of distribution of the coagulation markers plasma levels, respectively

		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
F1 + 2 (nM)	1 cutoff : 1.34	86	44	52	81
	2 cutoff : 1.77	80	80	66	71
TAT (µg/l)	1 cutoff : 2.5	79	41	49	73
	2 cutoff : 5.1	48	75	57	67
D-dimer (µg/l)	1 cutoff : 60	76	40	47	71
	2 cutoff : 129	48	75	57	67

predicts the absence of postoperative DVT during hospitalization with a sensitivity and a negative predictive value of 86 and 81%, respectively; however this information is useful in only 44% of the patients. The specificity of the test increases to 80%, with a slight decrease of sensitivity and negative predictive value (80 and 71% respectively), if the cutoff point is set at less than 1.77 nM. Therefore a low preoperative F1 + 2 concentration might delineate a certain proportion of individuals (about half), who will not develop DVT in high risk surgery.

The administration of antithromboembolic prophylaxis to our patients probably decreased the true incidence of venous thrombosis as compared to an untreated population; thus our data might underestimate the risk of DVT.

In conclusion, our findings raise the possibility that preoperative measurements of coagulation activation markers, in particular of F1 + 2, can be useful to predict DVT following total hip replacement. Even though these results look promising, more data on larger patient groups are needed to change current guidelines in the prophylaxis and surveillance for DVT following major orthopedic surgery.

REFERENCES

1. Bongard O., Wichy J., Peter R., Simonovska S., Vogel J. J., De Moerloose P., Reber G., Bounameaux H. D-dimer plasma measurement in patients undergoing major hip surgery: Use in the prediction and diagnosis of postoperative proximal vein thrombosis. *Thromb. Res.*, 1994, 74, 487-493.
2. Eriksson B. I., Kalebo P., Anthmyr B. A., Wadenvik H., Tengborn L., Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. *J. Bone Joint Surg.*, 1991, 73-A, 484-493.
3. Geerts W. H., Code K. I., Jay R. M., Chen E., Szalai J. P. A prospective study of venous thromboembolism after major trauma. *N. Engl. J. Med.*, 1994, 321, 1601-1606.
4. Ginsberg J. S., Brill-Edwards P., Panju A., Patel A., McGinnis J., Smith F., Dale I., Johnston M., Ofosu F. Preoperative plasma levels of thrombin-antithrombin III complexes correlate with the development of venous thrombosis after major hip or knee surgery. *Thromb. Haemost.*, 1995, 74, 602-605.
5. Haake D. A., Berkman S. A. Venous thromboembolic

- disease after hip surgery. *Clin. Orthop.*, 1989, 242, 212-231.
6. Hoek J. A., Nurmohamed M. T., Cate J. W., Buller H. R., Knipscheer H. C., Hamelnyck K. J., Marti R. K., Sturk A. Thrombin-antithrombin III complexes in the prediction of deep vein thrombosis following total hip replacement. *Thromb. Haemost.*, 1989, 62, 1050-1052.
 7. Mohr D. N., Silverstein M. D., Murtaugh P. A., Harrison J. M. Prophylactic agents for venous thrombosis in elective hip surgery. Meta-analysis of studies using venographic assessment. *Arch. Intern. Med.*, 1993, 153, 2221-2228.
 8. Ofosu F. Pre-operative plasma levels of thrombin-antithrombin III complexes correlate with the development of venous thrombosis after major hip or knee surgery. *Thromb. Haemost.*, 1995, 74, 602-605.
 9. Paiement G. D., Schutzer S. F., Wessinger S. J., Harris W. H. Influence of prophylaxis on proximal venous thrombosis formation after total hip arthroplasty. *J. Arthroplasty*, 1992, 7, 471-478.
 10. Planes A., Vochelle N., Fagola M. Total hip replacement and deep vein thrombosis. *J. Bone Joint Surg.*, 1990, 72-B, 9-13.
 11. Rocha E., Alfaro M. J., Paramo J. A., Canadell J. M. Preoperative identification of patients at high risk of deep vein thrombosis despite prophylaxis in total hip replacement. *Thromb. Haemost.*, 1988, 59, 93-95.
 12. Weitz J. I. Low-molecular-weight heparins. *N. Eng. J. Med.*, 1997, 10, 688-698.

SAMENVATTING

A. CORRADI, F. LAZZARO, E. COFRANCESCO, M. CORTELLARO, F. RAVASI, F. BERTOCCHI. Relatie van het plasma fragment 1 + 2 protrombine en het risico op flebotrombose na totale heupartroplastie.

Incidentie van flebotrombose na chirurgie op de heup kan worden teruggedrongen door een betere identificatie van de pre-operatieve risicofactoren. De auteurs hebben een studie uitgevoerd waarbij 159 patiënten voor een totale heupartroplastie met anti-coagulantetherapie werden nagegaan. Er werd nagekeken of een hypercoagulabiliteit aanwezig was voor de klassieke triade van Virchow. Er werd met de Elisa-techniek het plasmatisch niveau van 3 markers voor coagulatie gemeten: fragment 1 + 2 van de protrombine, de complexen trombine-antitrombine III en de D-dimeren. De metingen werden gecorreleerd met resultaten van de postoperatoire flebografie. Er was een verhoogd statistisch significante relatie tussen het pre-operatief fragment 1 + 2 niveau en de postoperatieve flebotrombose. Trombine-antitrombine en D-dimeren blijken minder predicatief

te zijn. Deze resultaten lijken aan te duiden dat de preoperatieve meting van coagulatie-activiteit nuttig zijn voor de preventie van flebotrombose na totale heupartroplastie.

RÉSUMÉ

A. CORRADI, F. LAZZARO, E. COFRANCESCO, M. CORTELLARO, F. RAVASI, F. BERTOCCHI. Relation entre le niveau plasmatique préopératoire des fragments 1+2 de la prothrombine et le risque de phlébothrombose après prothèse totale de hanche.

L'incidence des phlébothromboses après chirurgie de la hanche pourrait être réduite par une meilleure identification préopératoire des patients à haut risque. Les auteurs ont réalisé une étude portant sur 159 patients soumis à une arthroplastie totale de la hanche

et soumis à une anti-coagulation préventive, en recherchant la présence d'un état d'hypercoagulation, qui est un des éléments de la triade de Virchow prédisposant à la phlébothrombose profonde. Ils ont mesuré par des techniques de type ELISA les niveaux plasmatiques de trois marqueurs de l'activation de la coagulation : le fragment 1+2 de la prothrombine, les complexes thrombine anti-thrombine III, et les D-Dimères. Les mesures ont été corrélées avec les résultats de la phlébographie postopératoire. Les auteurs ont observé une corrélation élevée ($p < 0,001$) entre les niveaux plasmatiques préopératoires de F1+2 et le risque de phlébothrombose postopératoire. Les niveaux de TAT et de D-dimères apparaissaient moins prédictifs.

Ces résultats semblent indiquer que la mesure préopératoire des marqueurs de l'activation de la coagulation pourrait être utile pour prévoir les phlébothromboses profondes après arthroplastie totale de la hanche.