THE RELATIONSHIP OF D-DIMER LEVELS WITH RISK FOR DEVELOPING DEEP-VEIN THROMBOSIS AND/OR PULMONARY THROMBOEMBOLISM AFTER ORTHOPAEDIC TRAUMA SURGERY

Naeem MA, Usman M*, Latif MK, Aamir M*****

Department of Haematology, *Microbiology, **Medicine, ***Chemical Pathology, Combined Military Hospital, Abbottabad, Pakistan

Background: Deep venous thrombosis (DVT) and pulmonary embolism (PE) are common complications in trauma patients. Fibrin-related markers (FRMs), such as fibrin and fibrinogen degradation products (FDPs), D-dimer, and soluble fibrin (SF), are considered to be useful for the diagnosis of thrombosis (DVT). **Objective:** We report on 3-month follow-up of fibrinolytic activity after Orthopaedic Trauma Surgery (OTS). **Methods:** Patients who entered the study were divided into (group 1) patients who did not develop DVT/PE after OTS while patients who developed DVT/PE were included in (group 2). Blood samples were obtained on day of surgery and postoperative days 1, 7 and 30, and assayed for blood counts, C-reactive protein (CRP), and D-dimers. Demographic and clinical data were also collected. **Results:** Postoperative levels of D-dimers of both groups increased on day 1, and remained elevated on day 30. Postoperative levels of D-dimers on day 1, 7 and 30 were higher in group 2 ($p<0.05$). There were no differences in perioperative levels of CRP between groups, and they correlated with D-dimers both preoperatively and on day 30. Taken together, these data suggest that orthopaedic trauma surgery induced an activation of coagulation and fibrinolysis. This situation lasts at least as late as 30 days after surgery. **Conclusion:** The D-dimer levels were significantly higher in patients developing DVT/PE post OTS.

Keywords: D-dimer, DVT, Deep Vein Thrombosis, Pulmonary Embolism

INTRODUCTION

An activation of the fibrinolytic system in the first hours after removal of the pneumatic tourniquet has been described in orthopaedic trauma surgery. This effect is positive in so far as it reduces the risk of thrombo-embolism in orthopaedic surgery.[1] Deep venous thrombosis (DVT) and pulmonary embolism (PE) are common complications in trauma patients. These diagnoses can be difficult and expensive to make. Recent studies report that a negative D-dimer test excludes thrombotic complications. Fibrin-related markers (FRMs), such as fibrin and fibrinogen degradation products (FDPs), D-dimer, and soluble fibrin (SF), are considered to be useful for the diagnosis of thrombosis (DVT). However, the evidence for the making of a diagnosis of thrombosis based on FRMs is, as yet, not fully established.[2]

MATERIALS AND METHODS

Consecutive patients who underwent OTS and gave informed consent entered the study. Patients with haematological diseases or coagulation disorders, hepatic or renal diseases, those under oral anti-platelet or anti-coagulant therapy, having surgery or transfusion in the previous 3 months, or with known infection or malignancy at admission were excluded. All surgical procedures were performed under general anaesthesia by the same surgical team.

The anaesthesiologist estimated fluid administration (1000–1500 ml Ringer lactate) and blood losses, both at the operation theatre and in the anaesthesia recovery unit, and performed Allogenic Blood Transfusion (ABT). All patients stayed at the post-anaesthesia recovery unit for at least 2 hours before being transferred to the ward, where measurement of postoperative blood loss and decisions on postoperative transfusions were made by the attending surgeon. In this series of elderly patients who may tolerate anaemia poorly, transfusion was indicated when patient's Hb level fell below 8 g/dl or when patient presented symptoms of acute anaemia (hypotension, tachycardia, tachypnoea, dizziness, fatigue, etc.). For calculation of requirements for ABT, one unit of packed red cell was considered as a one blood unit.

Four blood samples were obtained from the patients: on the day of surgery (DS), before anaesthesia, and on post-operative days 1 (PO1), 7 (PO7) and 30 (PO30). Samples were assayed for blood counts (Sysmex KX-21, Japan), C-reactive protein (CRP, USA), and D-dimers (BCS, Germany). A set of demographic and clinical data was collected from all patients, including: age, gender, weight, height, volume, preoperative Hb, postoperative complications, and length of hospital stay. Total blood lost on PO7 was calculated according to the method described by Rosencher *et al.*[3]

Data were expressed as percentage (%) or as the Mean±SD *(n)*. Pearson's Chi-square test or was used for comparison of qualitative variables. Parametric Student's *t*-test was used for comparison of quantitative variables, after consideration of distributional characteristics. Statistical tests were performed using the SPSS 12.0 and $p<0.05$ was considered statistically significant.

RESULTS

Fifty consecutive OTS patients entering the study were divided into two groups, There were no differences regarding demographic data, total blood loss or postoperative infection rate between groups, but length of hospital stay was longer in group-2 when compared with that of group 1 and there were more American Society of Anaesthesiology (ASA) III patients in group-2 .

There were no differences in, perioperative Hb levels between groups 1 and 2, but preoperative and 30-day postoperative Hb levels were significantly lower in group 2 when compared with those of group 1 Preoperative plasma levels of D-dimers were within normal range (0–190 μg/L) in most patients 41/50, (82%). Compared with preoperative values, postoperative plasma levels of D-dimers increased on PO1, and remained elevated on PO3 of all patients. At all time points, these increases were more pronounced in patients who developed DVT/PE regardless of treatment (5–8 fold increase).

Preoperative serum levels of CRP were within normal range (0–8 mg/L) in most patients (36/50, 72%), and there was a significant correlation between preoperative D-dimer and CRP levels (r=0.239, p=0.013). Compared with preoperative values, postoperative serum levels of CRP increased significantly after 24 hours, and decreased thereafter without differences between groups However, on PO30, CRP levels remained above the normal range in 23 patients (46%), and again there was a significant correlation between D-dimer and CRP levels (r=0.234, p=0.030).

DISCUSSION

In May 2008 we implemented the D-dimer testing protocol for all patients who underwent OTS and gave informed consent entered the study. Patients with haematological diseases or coagulation disorders, hepatic or renal diseases, those under oral anti-platelet or anti-coagulant therapy, having surgery or transfusion in the previous 3 months, or with known infection or malignancy at admission were excluded. All surgical procedures were performed under general anesthesia by the same surgical team.[4]

On three months follow-up (May-July 2008) of fibrinolytic activity after orthopedic trauma surgery (OTS). Patients who entered the study were divided into (group 1) patients who did not develop DVT/PE after orthopedic trauma surgery (OTS) while patients who developed DVT/PE were included in (group 2).Blood samples were obtained on day of surgery and postoperative days 1, 7 and 30, and assayed for blood counts, C-reactive protein (CRP), and D-dimers.[5] Demographic and clinical data were also collected. Postoperative levels of D-dimers of both groups increased on day 1, and remained elevated on day 30. Postoperative levels of D-dimers on day 1, 7 and 30 were higher in group 2 (p<0.05). There were no differences in perioperative levels of CRP between groups, and they correlated with D-dimers both preoperatively and on day 30. Taken together, these data suggest that orthopedic trauma surgery induced an activation of coagulation and fibrinolysis. This situation lasts at least as late as 30 days after surgery. The D-dimer levels were significantly higher in patients developing DVT/PE post OTS.[6]

Venous thromboembolism is a relevant social and health care problem because of its high incidence among patients who undergo surgery (20–30% after general surgical operations and 50–75% after orthopaedic procedures), its pulmonary embolism-related mortality rate, and its long-term sequelae (post-thrombotic syndrome and ulceration), which may be disabling. The diagnostic work-up of patients with suspected pulmonary embolism (PE) has been optimized and simplified by the use of clinical decision rules (CDR), D-dimer (DD) testing and spiral computed tomography (s-CT).[7–9]

In a prospective randomized study D-dimer was analysed pre- and postoperatively in 206 consecutive patients undergoing hip arthroplasty during thrombo-prophylaxis with either a LMW heparin (Enoxaparin) or Dextran 70. Deep vein thrombosis (DVT) developed in 6 of 102 (6%) Enoxaparin and in 21 of 104 (20%) Dextran patients diagnosed by bilateral phelobography. In the Enoxaparin group heptest showed a significant increase from the pre- to the postoperative level opposed to a significant decrease in the Dextran group. Postoperative levels of D-dimer were significantly increased in both groups.[10] D-dimer was significantly higher in Dextran patients with DVT postoperatively compared with patients without DVT.[11,12]

Patients in whom DVT/PE was highly suspected were diagnosed by high-resolution multi-detector row computed tomography scanning (MDCT). Forty-nine knees in 46 patients with rheumatoid arthritis (RA, 24 knees) or D-Dimer measurement has been used as a simple, non-invasive test to rule out thromboembolic phenomena in patients at risk for deep venous thrombosis (DVT) and/or pulmonary embolism (PE).[13] Elevated D-Dimer level caused by tissue injury is believed to show a trend for gradual decrease to normal within the first three days after trauma.[14]

To study the effect of tissue injury on D-Dimer levels, we conducted a prospective measurement of D-Dimer levels in severely traumatized, high-risk patients for DVT or PE, starting within 24 hours after admission until disposition of the patient or to a total of 14 days of hospitalization.

Patients were observed clinically for development of thromboembolic phenomena, and were subjected to weekly surveillance using duplex scan of the lower extremities. Additional testing was done if requested by the attending trauma surgeon. A total of 21 patients were enrolled in the study. There were 17 males, and 4 females. Patients had a mean age of (42) with a range of (17–79), and a mean ISS score of (20) with a range of (4–50). Seven patients completed 3–9 days of testing. Fourteen patients had more than 10 days of testing. Nine patients completed 14 days of testing. In all patients, tissue injury resulted in increased levels of D-Dimer above a threshold (500 ηg/ml), below which DVT or PE can be ruled out. The increased levels failed to normalize even when testing was continued for 14 days. In our study, the increased D-Dimer levels induced by tissue injury failed to show a trend of gradual return to normal within three days after trauma, as currently believed. This, in our opinion, may eliminate our ability to use D-Dimer testing to rule out DVT or PE in a subset of severely traumatised patients in the early post trauma period. Although increased D-dimer and fibrinogen levels have been proved to be related with atrial fibrillation (AF) their evolution in the course of time remains unclear. The diagnostic work-up of patients with suspected pulmonary embolism (PE) has been optimized and simplified by the use of clinical decision rules (CDR), D-dimer (DD) testing and spiral computed tomography (s-CT).

To determine the utility of high quantitative D-dimer levels in the diagnosis of pulmonary embolism. D-dimer testing was performed in consecutive patients with suspected pulmonary embolism. We included patients with suspected pulmonary embolism with a high risk for venous thromboembolism, i.e., hospitalised patients, patients older than 80 years, with malignancy or previous surgery. Presence of pulmonary embolism was based on a diagnostic management strategy using a clinical decision rule (CDR), D-dimer testing and computed tomography. A total of 1515 patients were included with an overall pulmonary embolism prevalence of 21%. The pulmonary embolism prevalence was strongly associated with the height of the D-dimer level, and increased fourfold with D-dimer levels greater than 4000 ηg/ml compared to levels between 500 and 1000 ηg/ml. Patients with D-dimer levels higher than 2000 ηg/ml and an unlikely CDR had a pulmonary embolism prevalence of 36%.[15]

This prevalence is comparable to the pulmonary embolism likely CDR group. When D-dimer levels were above 4000 ηg/ml, the observed pulmonary embolism prevalence was very high, independent of CDR score. Strongly elevated D-dimer levels substantially increase the likelihood of pulmonary embolism.[16] Whether this should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels irrespective of CDR remains to be seen.[17]

We have advocated the use of a D-dimer assay to exclude the diagnosis of pulmonary embolism (PE) and deep venous thrombosis (DVT) in surgical and trauma patients suspected of having these diagnoses. Injury is known to increase D-dimer levels independent of thromboembolism. The purpose of this study was to assess the period after injury over which the D-dimer assay remains positive because of injury exclusive of thromboembolism. We prospectively sampled the plasma of severely injured patients for D-dimer using an enzyme-linked immunosorbent assay method at admission; at hours 8, 16, 24, and 48; and at days 3, 4, 5, and 6. Patients were then screened for DVT with a routine duplex Doppler at day 7. Patients were followed for PE, adult respiratory distress syndrome, and disseminated intravascular coagulation. One hundred fifty-four patients (mean Injury Severity Score of 23) underwent a total of 1,230 D-dimer assays. Twenty-six (17%) had thromboembolism.[18] Nine (6%) patients developed DVT, 2 (1%) developed PE, 13 (8%) developed disseminated intravascular coagulation, and 11 (7%) developed severe adult respiratory distress syndrome. None of the trauma patients with thromboembolism had a (false) negative D-dimer at or after the time of their thromboembolic complication. True-negative D-dimer results as a function of time from injury are: 0 hours, 18%; 8 hours, 16%; 16 hours, 17%; 24 hours, 22%; 48 hours, 37%; day 3, 34%; day 4, 32%; day 5, 30%; and day 6, 30%.[19,20] The negative predictive value of the assay was 100%. D-dimer levels were significantly higher in those who developed a thromboembolic complication than in those who did not (independent of Injury Severity Score).[21–23] These data serve to validate D-dimer as a means of excluding thromboembolism, specifically in patients with severe injury (100% negative predictive value). Before 48 hours after injury, however, the vast majority of these patients without thromboembolism had positive D-dimer assays. Because of the high false-positive rate early after severe injury, the D-dimer assay may be of little value before post injury hour.[24–26]

CONCLUSION

When combined with other tests of coagulation, D-dimer testing is useful in the diagnosis of disseminated intravascular coagulation. However, this diagnostic strategy may only be used safely when the clinical probability of thromboembolism is low to moderate.

REFERENCES

1. Milic DJ, Pejcic VD, Zivic SS, Jovanovic SZ, Stanojkovic ZA, Jankovic RJ, *et al.* Coagulation status and the presence of postoperative deep vein thrombosis in patients undergoing laparoscopic cholecystectomy. Surg Endosc 2007;21:1588–92.
2. Sohne M, Kruip MJ, Nijkeuter M, Tick L, Kwakkel H, Halkes SJ, *et al*. The Christoper Study Group. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. J Thromb Haemost 2006;4:1042–5.
3. Rosencher N, Shander A. Preoperative autologous blood donation. *Transfusion Alternatives in Transfusion Medicine* 2006;8: 29–34
4. Wada H, Sakuragawa N. Are fibrin-related markers useful for the diagnosis of thrombosis? Semin Thromb Hemost 2008;34(1):33–8.
5. Erem C, Kocak M, Hacihasanoglu A, Yilmaz M, Saglam F, Ersoz HO. Blood Coagulation, Fibrinolysis and Lipid Profile in Patients with Primary Hyperparathyroidism: Increased Plasma Factor VII and X Activities and D-Dimer Levels. Exp Clin Endocrinol Diabetes 2008;116:619–24.
6. Borris LC, Sørensen JV, Lassen MR, Walenga JM, Fareed J, Jørgensen LN, *et al.* Components of coagulation and fibrinolysis during thrombosis prophylaxis with a low molecular weight heparin (Enoxaparin) versus Dextran 70 in hip arthroplasty. Thromb Res 1991;63(1):21–8.
7. Chen CJ, Wang CJ, Huang CC. The value of D-dimer in the detection of early deep-vein thrombosis after total knee arthroplasty in Asian patients: a cohort study. Thromb J 2008;6:5.
8. Yoshitaka T, Abe N, Minagawa H, Date H, Sakoma Y, Nishida K, *et al.* Disease-specific screening for deep venous thrombosis and pulmonary thromboembolism using plasma D-dimer values after total knee arthroplasty. Mod Rheumatol 2008;18(4):359–65.
9. Milic DJ, Pejcic VD, Zivic SS, Jovanovic SZ, Stanojkovic ZA, Jankovic RJ, *et al*. Coagulation status and the presence of postoperative deep vein thrombosis in patients undergoing laparoscopic cholecystectomy. Surg Endosc 2007;21(9):1588–92.
10. Terao M, Ozaki T, Sato T. Diagnosis of deep vein thrombosis after operation for fracture of the proximal femur: comparative study of utrasonography and venography. J Orthop Sci 2006;11(2):146–53.
11. Codine P, Barbotte E, Denis-Laroque F, Lansac H, Dupetit T, Pradies F, *et al.* C-reactive protein, leukocyte count and D-dimer monitoring after orthopedic surgery: early diagnosis of infectious or thromboembolic complications. Part two: does d-dimer measurement contribute to the diagnosis of postoperative venous thromboembolism? Ann Readapt Med Phys 2005;48:598–602.
12. Nishiguchi M, Takamura N, Abe Y, Kono M, Shindo H, Aoyagi K. Pilot study on the use of tourniquet: a risk factor for pulmonary thromboembolism after total knee arthroplasty. Thromb Res 2005;115:271–6.
13. Habermann B, Hochmuth K, Hovy L, Scharrer I, Kurth AH. Management of haemophilic patients with inhibitors in major orthopaedic surgery by immunadsorption, substitution of factor VIII and recombinant factor VIIa (NovoSeven): a single centre experience. Haemophilia 2004;10:705–12.
14. Fujisawa M, Naito M, Asayama I, Kambe T, Koga K. Effect of calf-thigh intermittent pneumatic compression device after total hip arthroplasty: comparative analysis with plantar compression on the effectiveness of reducing thrombogenesis and leg swelling.J Orthop Sci 2003;8:807–11.
15. Shiota N, Sato T, Nishida K, Matsuo M, Takahara Y, Mitani S, *et al*. Changes in LPIA D-dimer levels after total hip or knee arthroplasty relevant to deep-vein thrombosis diagnosed by bilateral ascending venography. J Orthop Sci 2002;7:444–50.
16. Kubo T, Kitajima I, Makinodan A, Niratsuka S, Inoue S, Otsuka G, *et al*. Fibrin monomer could be a useful predictor of pulmonary embolism after total hip arthroplasty: preliminary report. J Orthop Sci 2001;6:119–22.
17. Abraham P, Ternisien C, Hubert L, Pidhorz L, Saumet JL. Does venous microemboli detection add to the interpretation of D-dimer values following orthopedic surgery? Utrasound Med Biol 1999;25:637–40.
18. Han CD, Shin DE. Postoperative blood salvage and reinfusion after total joint arthroplasty. J Arthroplasty 1997;12:511–6.
19. Nelson CL, Hickmon SG, Skinner RA. Treatment of experimental osteomyelitis by surgical debridement and the implantation of bioerodable, polyanhydride-gentamicin beads. J Orthop Res 1997;15:249–55.
20. Dunn ID, Hui AC, Triffitt PD, Crozier AE, Gregg PJ, Sinclair ME, Armstrong AL, Mitchell VE. Plasma D-dimer as a marker for postoperative deep venous thrombosis. A study after total hip or knee arthroplasty. Thromb Haemost 1994;72:663–5.
21. Terao M, Ozaki T, Sato T Diagnosis of deep vein thrombosis after operation for fracture of the proximal femur: comparative study of ultrasonography and venography. J Orthop Sci 2006;11:146–53.
22. Dougu N, Takashima S, Sasahara E, Taguchi Y, Toyoda S, Hirai T, *et al.* Differential diagnosis of cerebral infarction using an algorithm combining atrial fibrillation and D-dimer level. Eur J Neurol 2008;15(3):295–300.
23. Yoshitaka T, Abe N, Minagawa H, Date H, Sakoma Y, Nishida K, *et al.* Disease-specific screening for deep venous thrombosis and pulmonary thromboembolism using plasma D-dimer values after total knee arthroplasty. Mod Rheumatol 2008;18(4):359–65.
24. Johna S, Cemaj S, O'Callaghan T, Catalano R. Effect of tissue injury on D-Dimer levels: a prospective study in trauma patients. Med Sci Monit 2002;8(1):CR5–8.
25. Wang TL, Hung CR, Chang H Evolution of plasma D-dimer and fibrinogen in witnessed onset of paroxysmal atrial fibrillation. Cardiology 2004;102(2):115–8.
26. Vermeer HJ, Ypma P, van Strijen MJ, Muradin AA, Hudig F, Jansen RW, *et al.* Exclusion of venous thromboembolism: evaluation of D-Dimer PLUS for the quantitative determination of D-dimer. Thromb Res 2005;115(5):381–6.

Address for Correspondence:

Dr. Muhammad Abdul Naeem, Consultant Haematologist, Combined Military Hospital Abbottabad, Pakistan. Cell: +92-346-5439851

Email: bugsgallian@yahoo.com