Abstract The prognosis of venous thromboembolism is considerably influenced by an accurate and fast diagnosis. Although the role of D-dimer testing in the diagnosis of suspected venous thromboembolism is well established for outpatients, there is controversial evidence on the clinical usefulness of its measurement in surgical patients. In order to recognize patterns of variation of D-dimer following surgery and identify potential pitfalls in prediction of venous thromboembolic complications, plasma D-dimer was assayed in 30 patients undergoing major elective hip surgery and 20 patients undergoing laparoscopic cholecystectomy for acute cholecystitis. The postoperative variation of plasma D-dimer differed widely between the two subgroups. Patients undergoing laparoscopic cholecystectomy showed D-dimer concentrations persistently increased from the baseline to the 15th postoperative day, whereas patients undergoing hip surgery were characterized by a double peak, on the 1st and 7th postoperative days. Mean inter-individual daily coefficient of variations of plasma D-dimer throughout the postoperative period were 49% (range 39%–61%) for laparoscopic cholecystectomy and 101% (range 72%–156%) for orthopedic surgery. The markedly heterogeneous fluctuation of plasma D-dimer suggests that the postoperative activation of the hemostatic system depends on the type and time since surgery, thus limiting the clinical usefulness of D-dimer testing in the diagnostic approach to postoperative venous thromboembolism.

Key words D-dimer • Venous thromboembolism • Surgery

Introduction

Venous thromboembolism (VTE) is a major cause of illness, especially in hospitalized patients; the mortality rate is high and recurrent events occur rather frequently. VTE is a multifactorial disease; among the major predisposing factors, surgery plays a predominant role [1]. Although the introduction of adequate prophylactic regimens is effective in limiting the overall incidence of symptomatic VTE, the increased rate of thromboembolic events still remains a source of concern [2].

The diagnostic approach to VTE is puzzling [3]. The outcome of patients with VTE depends on a rapid and accurate diagnosis, due to the risk of underdiagnosis or overdiagnosis; consequently, reliable and fast diagnostic protocols are essential [4]. Recently, several clinically validated algorithms based on noninvasive diagnostic testing were proposed for outpatients. Clinical examination, plasma D-dimer (DD) measurement, ultrasonography, and lung scan are the hallmarks of most diagnostic protocols, an approach that simplifies and reduces the expense of more-intricate, risky, and expensive management strategies [5, 6]. Owing to the analytical sensitivity of plasma DD, it is now widely accepted that a value less than a given threshold rules out the presence of concurrent thrombotic pathologies [6]. However, due to the low analytical specificity, as DD concentrations are frequently raised nonspecifically in patients under investigation for suspected VTE, the analytical efficiency of DD-based diagnostic strategies may be rather limited in surgical patients [7]. In order to recognize the pattern of changes of DD following surgical operations and identify potential pit-
falls in VTE prediction, plasma DD was measured in surgical patients undergoing laparoscopic cholecystectomy or elective fracture hip surgery.

Patients and methods

Patient selection

The initial part of the study included 32 consecutive patients undergoing elective hip surgery for traumatic hip fracture (12 males, 20 females, mean age 46.6±12.5 years) and 20 consecutive patients undergoing laparoscopic cholecystectomy for acute cholecystitis (8 males, 12 females, mean age 42.1±14.6 years). Patients undergoing elective hip surgery received identical thromboprophylaxis, consisting of graduated compression stockings and one daily subcutaneous injection of low molecular weight heparin nadroparin calcium (Fraxiparina, Sanofi-Winthrop, Gentilly, France) in a fixed, weight-adjusted dosage. Patients undergoing laparoscopic cholecystectomy did not receive thromboprophylaxis. Postoperative mobilization was achieved in 24 h in the laparoscopic cholecystectomy group and in 72 h in the elective hip surgery group. The occurrence of VTE complications was assessed by clinical examination and bilateral color Doppler ultrasonography of the leg veins from the 15th to the 18th postoperative days. In agreement with the prevalence observed in earlier reports [2, 8], 2 patients belonging to the hip surgery subgroup (2/32, 6.3%) developed VTE in the postoperative period and were excluded from the study.

Laboratory procedures

Blood samples were collected after an overnight fast by venipuncture into siliconized vacuum tubes containing 0.123 mol/l sodium citrate (Becton-Dickinson, Oxford, UK). After centrifugation at 3,000 g for 15 min at 10°C, plasma was separated and stored at -70°C until measurement. Plasma DD was serially measured using Vidas DD, a rapid and quantitative automated enzyme-linked immunosorbent assay with fluorescent detection (bioMerieux, Marcy l’Etoile, France), performed on the Mini Vidas immunoanalyzer (bioMerieux). The reference interval is reported to be 68–494 ng/ml [9]. All measurements were performed in duplicate within a single analytical session, and final results were averaged. Inter-assay coefficient of variation (CV) of Vidas DD is reported to be lower than 5% [9]. DD was measured preoperatively on the day before the operation (baseline value), and on the following 1st, 3rd, 5th, 7th, and 15th postoperative days. Significance of differences between baseline and postoperative DD concentrations were assessed by Student’s t-test; P<0.05 was considered statistically significant.

Results

The patterns of changes of plasma DD concentrations during the 15 days’ postoperative follow-up are shown in Fig. 1. The fluctuation of DD in plasma was rather different between the two subgroups of patients, suggesting that the activation of the hemostatic system depends on the type of surgery. Patients undergoing laparoscopic cholecystectomy showed DD concentrations persistently increased from the baseline, reaching the maximum value 7 days following surgery. All mean values, from day 1 through 15, were statistically different from those at baseline. Patients undergoing reconstructive hip surgery showed a significantly stronger activation of the coagulation system preoperatively and during the following postoperative days. In particular, DD concentrations increased substantially on the 1st postoperative day, fell on the 3rd day, and then showed a second peak on the 5th postoperative day. Although DD levels on the 15th postoperative day were comparable to those at baseline, they still largely exceeded the conventional diagnostic threshold for outpatients (500 ng/ml). Mean inter-individual

![Fig. 1 Pattern of changes of plasma D-dimer in patients undergoing laparoscopic cholecystectomy (a) and elective fracture hip surgery (b). Results are given as mean±standard deviation. *P<0.05, **P<0.01](image-url)