Kinetics of D-dimer after general surgery

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D-dimers may be elevated after surgery. However, the kinetics of postoperative D-dimers remains unknown hampering the use of D-dimer testing in surgical patients with suspected venous thromboembolism. D-dimer levels were prospectively measured in 154 patients after general surgery at predefined time points (kinetics were determined in an initial cohort of 108 patients; for validation, these findings were applied to a second cohort of 46 patients). Clinical factors influencing the peak of D-dimers were analyzed using multivariate regression. Surgical operations were stratified based on severity (type I: not entering abdominal cavity; type II: intraabdominal; type III: retroperitoneal/liver surgery). D-dimer levels increased postoperatively reaching a peak on day 7. After type I surgery, peak D-dimer levels did not exceed normal range (300 ng/ml, 100–500). After type II procedures, peak D-dimer level was 1500 ng/ml (200–7800) and returned to normal values after 25 days (±14). Peak level was 4000 ng/ml (500–14 400) after type III surgery normalizing within 38 days (±11). Clearance of D-dimer was exponential after having reached the peak with 6.0% per day (95% confidence interval 4.8–7.1%). By this clearance, D-dimer values could be adequately predicted in the validation cohort after day 7 ($r^2 = 0.63$). Peak D-dimer levels were independently influenced by the type of surgery ($P<0.001$), the operation time ($P<0.001$) and by preoperatively elevated D-dimer levels ($P<0.001$). Based on this data, duration of postoperative D-dimer elevation after abdominal surgery is predictable. This study indicates for the first time when D-dimers may be used again in the diagnostic algorithm for venous thromboembolism exclusion after surgery in patients with low or moderate clinical probability. *Blood Coagul Fibrinolysis* 20:347–352 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Venous thromboembolism (VTE), comprising deep venous thrombosis and pulmonary embolism, is associated with substantial morbidity and mortality. Surgery has been identified to be a major risk factor for VTE. Incidence of symptomatic VTE in patients after general surgery varies between 0.3 and 2.8% [1,2] depending on the type of surgery, the presence of cancer and the patients' age [3]. The incidence of asymptomatic VTE may reach 37% in cancer patients undergoing surgery [4]. Of note, 40–75% of VTE after surgery occur after patients' discharge [5,6]. This proportion may even increase as the duration of hospital stay after surgery further decreases.

The diagnosis of VTE remains challenging. D-dimers, degradation products of a cross-linked fibrin clot, are sensitive markers with a high negative predictive value for the diagnosis of VTE, but they are not specifically hampering the use of D-dimers to diagnose VTE [7]. In nonhospitalized patients with a low or moderate clinical probability as assessed by the model of Wells *et al.* [8] (Table 1) and with negative D-dimer testing, VTE may be excluded without further diagnostic imaging [7]. This strategy holds for as many as 40% of patients with suspected VTE and therefore simplifies the diagnostic management of these patients [7].

However, D-dimer levels were found to be elevated after various surgical procedures independent of the occurrence of VTE [9–12]. As the postoperative kinetics of D-dimers remains unknown, uncertainty exists regarding which time-point D-dimer may be used again after surgery as part of the diagnostic algorithm in cases of suspected VTE. Therefore, the aim of the present study was to evaluate the pattern of postoperative D-dimer alterations and to determine the clinical factors influencing the extent of the D-dimer elevation after abdominal surgery.

Material and methods

Study design

This prospective study was conducted to evaluate the kinetics of D-dimer after abdominal surgery. The kinetics was first determined in an initial cohort of patients (study cohort) and then applied to a second cohort of patients (validation cohort). The influence of

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Table 1 Clinical model for assessment of deep vein thrombosis

Clinical finding	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recent immobilization > 3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of DVT	−2

Adapted from [8]. Clinical probability for DVT calculated as follows: high (3); moderate (1 or 2); low (0). DVT, deep vein thrombosis.

different parameters on postoperative D-dimer levels was studied using univariate and multivariate analyses. The study was approved by the Ethics Committee of the institution and was registered at clinicaltrials.gov (NCT00450528).

Study population

Between January 2007 and July 2007, 154 patients undergoing abdominal surgery at our institution were included in the study, 108 in the study cohort and 46 in the validation cohort. Informed consent was obtained from all participants. Exclusion criteria were age less than 18 years, pregnancy, oral anticoagulation, history of former VTE and preoperative concomitant inflammatory diseases (e.g. sepsis, pneumonia). Additionally, patients were only allowed to participate in one single scientific study. Patients, who received fresh frozen plasma or fibrinogen during or after surgery or who had to be resubmitted to the operating theatre because of a complication, were secondarily excluded from the study. All patients received low molecular weight heparin (LMWH) once daily (Fragmin, dalteparin sodium, Pharmacia and Upjohn, Dubendorf, Switzerland; 5000 units subcutaneous) during their hospital stay, starting the evening before surgery. Additionally, graded compression stockings were used for all patients during the entire hospital stay. All patients were clinically evaluated at discharge to exclude VTE.

Determination of D-dimers

In the first phase, plasma D-dimers levels were determined preoperatively (day 0) and at various time points after surgery (day 1, 3, 5, 7, 10, 14, and weekly thereafter until D-dimer values returned to normal). After hospital discharge, blood samples were taken in the outpatient clinic. A value of less than 500 ng/ml or equal was considered as normal. D-dimers were analyzed using a quantitative enzyme-linked immunosorbent assay (ELISA) (VIDAS D-dimer; bioMérieux, Geneva, Switzerland) as previously described [13].

Stratification of surgical procedures, patients' risk and surgical morbidity

Surgical operations were stratified based on the degree of severity (type I: superficial surgery not opening the abdominal cavity such as open hernia repairs; type II: intraabdominal procedures such as colon resections; type III: retroperitoneal surgery such as pancreatic or esophageal resections and liver surgery) as previously defined [14]. Preoperative patients' risk was estimated by means of the grading systems of the American Society of Anesthesiologists (ASA) [15], the Nutrition Risk Score [16], and the Charlson Risk Index (CRI) [17]. The CRI is a comorbidity measure that contains a list of 19 different comorbidities. A numerical value from 1 to 6 is assigned to each of the comorbidities and the sum of these values reflects the CRI. In patients with a CRI of at least 3, mortality was shown to be doubled after surgery [18].

Statistical analyses

Continuous data are presented as mean ± standard deviation or median (range) and are compared between groups using the Mann–Whitney test or Kruskal–Wallis test in cases appropriate. Spearman rank correlations were used to analyze correlations between continuous variables. Categorical data are presented as number with percentage and are compared between groups using the χ^2 test [two degrees of freedom (DF) with the exception of type of surgery and ASA] or Fisher's exact test in cases appropriate. A logarithmic transformation of D-dimer values was used to approach a normal distribution. Analysis of covariance for repeated measures was applied to transformed data to analyze degradation over time. Paired *t*-tests were performed to compare values between days, and unpaired *t*-tests and analysis of variation (ANOVA) were used to compare values between groups. Box plots are given with medians and interquartile ranges (IQR). Outliers are indicated by open dots and asterisks: 'Extreme' outliers or those which lay more than three times the IQR (3 IQR) to the left and right from the first and third quartiles, respectively, are indicated by the presence of an asterisk. 'Mild' outliers – that is, those observations that lay more than 1.5 times the IQR from the first and third quartile, but are not extreme outliers, are indicated by the presence of a open dot. Single observations are indicated by a bar. SPSS 13.0 (SPSS, Inc., Chicago, Illinois, USA) was used for statistical analyses. Two-sided P values less or equal to 0.05 are considered statistically significant.

Results

Patient demographics

Informed consent has been obtained from 172 patients; 18 patients had to be excluded after surgery due to reoperation because of a complication (13 patients) or due to perioperative transfusions of fresh frozen plasma (five patients). A total of 154 patients were finally included in the study (108 as study cohort and 46 as

Table 2 Patient characteristics

	Overall $n=154$	Study cohort $n=108$	Validation cohort $n=46$	P
Age; years (SD)	55.1 (±14.5)	55.5 (±14.4)	54.4 (±14.9)	0.98
Female patients, *n* (%)	70 (45.5)	49 (45.4)	21 (45.7)	0.91
D-dimer preoperative > 500 ng/ml; *n* (%)	36 (23.4)	22 (20.4)	14 (30.4)	0.12
Length of surgery; min (range)	180 (25–480)	180 (25–480)	240 (40–450)	0.04
Blood loss, ml (range)	100 (0–2000)	100 (0–2000)	150 (0–2000)	0.10
Length of hospitalization; days (range)	8 (1–90)	8 (2–90)	8 (1–64)	0.80
Laparoscopic procedures; *n* (%)	63 (40.9)	49 (45.4)	14 (30.4)	0.06
Cancer; *n* (%)	59 (38.3)	35 (32.4)	24 (52.2)	0.03
Type of surgery				0.78
Type I; *n* (%)	20 (13.0)	15 (13.9)	5 (10.9)	NA
Type II; *n* (%)	66 (42.9)	46 (42.6)	20 (43.5)	NA
Type III; *n* (%)	68 (44.1)	47 (43.5)	21 (45.7)	NA
ASA				0.93
ASA I; *n* (%)	30 (19.5)	22 (20.4)	8 (17.4)	NA
ASA II; *n* (%)	82 (53.2)	57 (52.8)	25 (54.3)	NA
ASA III; *n* (%)	42 (27.3)	29 (26.8)	13 (38.3)	NA

Types of surgery: I, without opening of abdominal cavity; II, abdominal procedures w/o retroperitoneal/liver surgery; III: retroperitoneal/liver surgery. ASA, American Society of Anesthesiologists; NA, not available.

validation cohort); Table 2 shows the patients characteristics. Mean age was 55.1 years (±14.5) with 45.5% female participants in the entire patient cohort. Cancer was present in 38.3% of the patients. Patients (19.5%) were estimated to be grade I according to the ASA, 53.2% of grade II and 27.3% of grade III. Few of the surgical procedures (40.9%) were performed laparoscopically. Thirteen percent of the procedures comprised type I surgery, 42.9% were type II and 44.1% type III procedures. Median duration of surgery was 180 min (25–480), median blood loss was 100 ml (0–2000) and median length of hospitalization was 8 days (1–90). Surgical morbidity rate was 22.7% (35/154). Of note, none of the patients presented with clinical signs or symptoms of VTE during hospitalization or during follow-up, and none of them was readmitted to the hospital with symptomatic VTE.

There was no difference between the study cohort and the validation cohort regarding age ($P=0.98$), blood loss ($P=0.10$), preoperative D-dimer levels ($P=0.12$) and length of hospitalization ($P=0.80$). However, length of surgery was significantly longer in the patients used for validation ($P=0.04$) with more patients operated on for cancer ($P=0.03$).

Kinetics of D-dimer

D-dimer level before surgery was 290 ng/ml (100–3800). In 34 out of 154 (22.1%) patients, D-dimer levels were found to be above normal values already before surgery. Malignant disease and age were significantly associated with an elevated D-dimer before surgery ($P=0.01$ and 0.02, respectively). After surgery, D-dimer levels increased postoperatively reaching a peak on day 7 ($P\leq 0.001$ vs. all other days except day 5). After type I surgery, peak D-dimer levels did not exceed normal range (300 ng/ml, 100–500). Peak D-dimer level after type II procedures was 1500 ng/ml (200–7800) and returned to normal values after a period of 25 days (±14). After type III surgery, peak D-dimer level was 4000 ng/ml (500–14 400) and normalized within 38 days (±11). Forty-three out of 46 patients with a type II procedure and 39 of 47 patients undergoing a type III procedure, respectively, had D-dimer values within normal range after 25 days. After 38 days, D-dimer values were normal in all of the patients who underwent type II procedures and in 44 of 47 patients with a type III procedure.

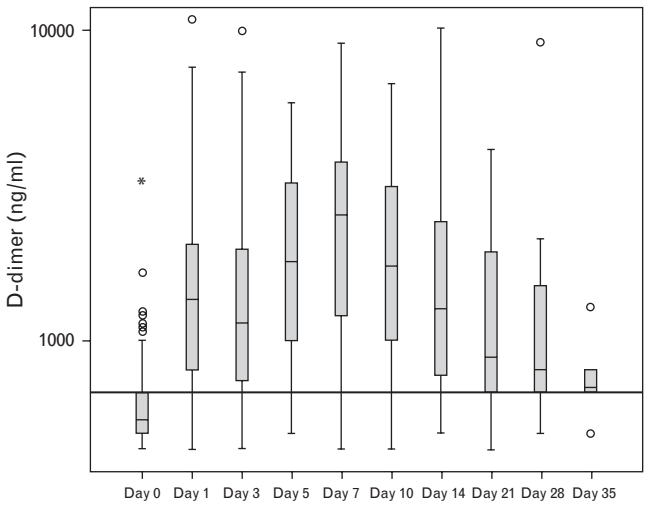
Degradation of D-dimer was exponential after having reached the peak with a clearance of 6.0% per day [95% confidence interval (CI) 4.8–7.1%] in the study cohort. By this clearance, D-dimer values could be adequately predicted in the patients of the validation cohort after determination of the peak D-dimer level ($r^2=0.72$ on a log scale). Clearance in the validation cohort was similar with 6.7% per day (95% CI 2.4–10.4%; $P=0.65$). Daily clearance of the entire patient cohort was 6.1% (95% CI 4.9–7.2%). Hence, half-life time of postoperative D-dimers was 11 days. The kinetics of D-dimers after surgery is shown for the entire patient cohort for all procedures (Fig. 1) and stratified by surgical type (Fig. 2).

Determinants of peak D-dimer levels

In univariate analyses, peak D-dimer was significantly determined by age ($P<0.001$), duration of surgery ($P<0.001$), blood loss ($P<0.001$), peak levels of C-reactive protein ($P<0.001$), preoperative D-dimer levels (greater than normal; $P<0.001$), length of hospitalization ($P<0.001$), type of surgery ($P<0.001$), the Nutrition Risk Score ($P<0.001$), the CRI ($P<0.001$), malignant disease ($P<0.001$), surgical technique (open vs. laparoscopic; $P<0.001$) and the ASA scoring ($P=0.02$).

By multivariate regression analysis of univariate significant parameters, duration and type of surgery ($P<0.001$,

Fig. 1



D-dimer values before (day 0) and after general surgery ($n = 154$).

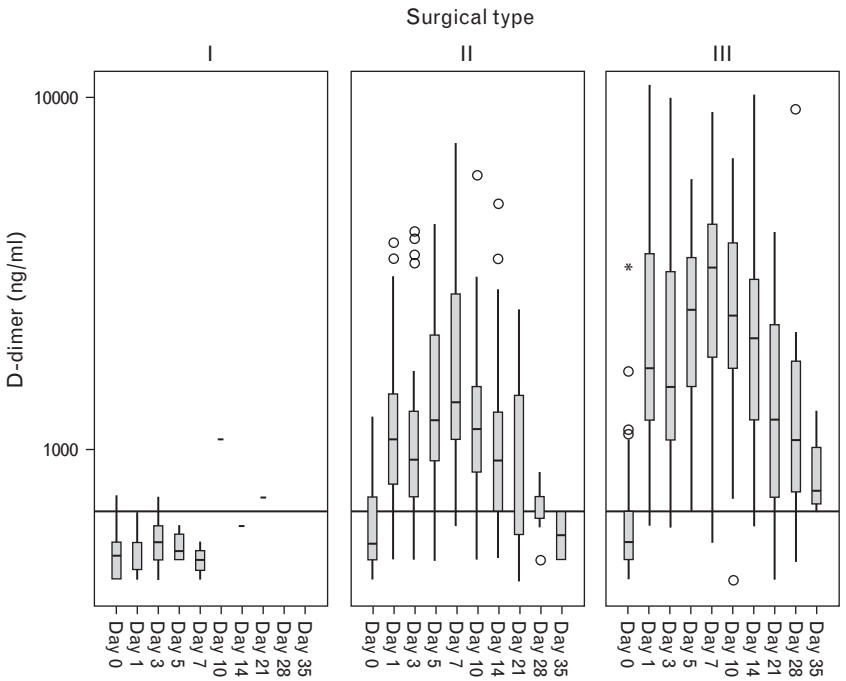
$\beta = 0.233$, $r^2 = 0.44$ and $P < 0.001$, $\beta = 0.338$, $r^2 = 0.38$) and preoperative D-dimer levels (greater than normal; $P < 0.001$, $\beta = 0.278$, $r^2 = 0.16$) were identified as independent determinants of peak D-dimer levels. By taking all independent risk factors into account, the prediction of the D-dimer levels could be markedly improved ($r^2 = 0.63$; Fig. 3) compared with the predictive capacity of each factor alone.

Discussion

Kinetics of D-dimer is largely unknown limiting the use of D-dimer testing for VTE exclusion after surgery. This is the first study showing the postoperative kinetics of D-dimers after abdominal surgery. D-dimer levels peak on the 7th postoperative day determined by the duration and the type of surgery as well as elevated preoperative D-dimer levels. After having reached the peak, D-dimers decrease with a rate of 6% per day, irrespective of the surgical type. On the basis of these findings, the duration of D-dimer elevation after surgery might be estimated for each patient.

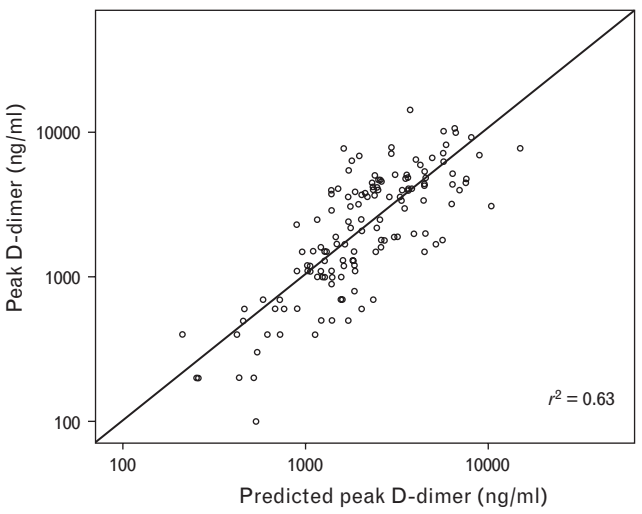
D-dimer testing in combination with clinical judgment has been shown to be cost effective in the diagnostic algorithm of VTE in the outpatient setting due to its high negative predictive value. The lack of specificity [7], however, prevents its use in the diagnosis of VTE particularly for patients after surgery. Despite prophylaxis with LMWH, compression stockings and physical therapy, VTE remains a challenging problem after surgery. Incidence of symptomatic VTE is reported to be 3% in cancer patients undergoing abdominal surgery [3] with most of the VTE occurring after patients' discharge [5,6]. Activation of the coagulation/ fibrinolysis system is well described in surgical patients [9–12]

Fig. 2



D-dimer values before (day 0) and after surgery stratified by surgical type.

Fig. 3



Correlation between predicted and measured peak D-dimer levels (multivariate regression model).

leading to an increased risk of VTE [19]. Alterations in the coagulation induced by the surgical trauma have been shown to persist for 4 weeks after hip replacement [20] and for more than 7 weeks in patients after coronary bypass surgery [21]. In abdominal surgery, D-dimer has been shown to rise after open [11] and laparoscopic cholecystectomy [9,11], after open and laparoscopic gastric bypass surgery [12] and after a selection of abdominal procedures [22] with a maximal observation time of 2 weeks [9,22]. However, no comprehensive data are available so far regarding the kinetics of D-dimers in postoperative patients without symptomatic VTE. We demonstrate that D-dimers peak at day 7 after surgery and, thereafter, are cleared irrespective of the type of surgery as well as the occurrence of complications not requiring intervention. The calculated clearance of the D-dimer (6% per day in the study cohort) could be validated by the second cohort of patients (validation cohort). D-dimers normalized within 25 and 38 days after type II and type III procedures, respectively. Only 3% of the patients showed a D-dimer level above the normal range 5 weeks after those procedures.

Our study reveals that D-dimers after minor surgery (type I procedures) do not increase. However, opening of the peritoneum leads to an increase of D-dimer levels depending on the duration of surgery, the invasiveness of the operation (type II vs. type III surgery) and elevated D-dimer levels. Interestingly, parameters such as age or malignancy did not influence the D-dimer levels after surgery – a finding, which seems to be in contrast to the literature [23,24]. This discrepancy might be explained by the fact that most of these studies focus on nonsurgical patients and by the lack of multivariate analyses to determine independent predictive factors of D-dimer elevation. However, malignant disease and age were associated in our study with increased preoperative D-dimer levels.

Beside its role as part of the diagnostic algorithm, D-dimer recently emerged as possible predictive factor for VTE [25,26]. There is evidence that D-dimer levels after surgery might be used to estimate the patients' risk for the development of postoperative VTE [26]. Hence, determination of postoperative D-dimer levels might be used to identify the patients who may benefit from extended thromboprophylaxis. In general surgery, four clinical trials have investigated the use of extended prophylaxis beyond the period of hospitalization following general surgery demonstrating a significant reduction of VTE with prolonged thromboprophylaxis [27–30]. On the basis of these studies, posthospital discharge prophylaxis with LMWH is suggested for high-risk general surgery patients, especially for patients after major cancer surgery [31]. However, high-risk patients are poorly defined, and the duration of the hypercoagulable state after general surgery remains elusive. Our study evaluated the duration of the activated coagulation/fibrinolysis system after abdominal surgery by elevated D-dimer levels, which might help to define the reasonable duration of postoperative thromboprophylaxis. We demonstrate that D-dimer levels are elevated for up to 6 weeks after major abdominal surgery. This finding may well correspond to the data from orthopedic surgery showing that extending thromboprophylaxis with LMWH for 4–5 weeks significantly reduces the incidence of VTE in patients undergoing total knee or hip replacement [32,33]. However, data from orthopedic surgery may not be directly transferred to general surgery, and the correlation between postoperative D-dimer levels and the risk of VTE has not yet been established.

Some considerations have to be made while interpreting our results. First, we did not perform routine duplex sonography or venography to exclude asymptomatic VTE after surgery. However, the focus of the study was to analyze D-dimer kinetics in patients without symptomatic VTE in order to apply the conclusions of this study to the vast majority of surgical patients that do not suffer from symptomatic VTE. Of note, none of the patients suffered from symptomatic VTE during follow-up. Second, only one assay was used for the measurement of D-dimers. Substantial variation has been described between different analytical methods to determine D-dimer levels [34]. However, quantitative rapid ELISA (VIDAS), as used in this study, has been identified as one of the most sensitive assay available [34].

In conclusion, this is the first report demonstrating the kinetics of D-dimers after abdominal surgery in an average surgical population. It allows estimating at which

point in time D-dimers reach normal values in asymptomatic patients after surgery. This might have an important clinical implication: it indicates when D-dimers may be used again in the diagnostic algorithm for VTE exclusion after surgery in patients with low or moderate clinical probability. After type I operations, D-dimer testing can be utilized after surgery in cases of suspected VTE without a lag phase whereas it appears futile after intraabdominal procedures (type II surgery) for a time span of 4 weeks and for 5–6 weeks after major abdominal surgery (type III surgery).

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