Prediction of Deep Vein Thrombosis after Total Knee Arthroplasty with Preoperative D-Dimer Plasma Measurement

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Background: *Despite prophylaxis, deep vein thrombosis (DVT) still occurs frequently after elective knee surgery. Hence, it would be helpful if the high-risk DVT patients could be identified before surgery so the adequate prophylaxis could be given. A normal plasma D-dimer level effectively rules out acute DVT patients who were classified as having low clinical probability. In many studies, one coagulation activation marker was measured to observe their role in preoperative prediction of DVT after major hip or knee surgery. In this study, the preoperative plasma level of D-dimer in patients undergoing total knee arthroplasty (TKA) was collected, and correlated with the results of postoperative venography.*
Objective: *To determine whether levels of D-dimer in plasma, taken two weeks preoperatively, predicts the development of DVT in patients undergoing TKA.*
Material and Method: *Fifty-nine consecutive patients undergoing TKA were seen in a preoperative clinic two weeks prior the surgery and had blood taken for measurement of plasma D-dimer. After surgery, they did not receive prophylaxis anticoagulant. Ascending contrast venography of both lower extremities was performed in all cases between the 6th-10th postoperative day or earlier if clinical symptoms occurred.*
Results: *Plasma D-dimer was measured preoperatively in 59 patients undergoing TKA. DVT was detected by venography in 31 (53%) patients. At a cutoff or 500 ng/ml, the sensitivity, specificity, positive and negative predictive values of the preoperative D-dimer concentration for the development of subsequent DVT were 58%, 46%, 55%, and 50%, respectively.*
Conclusion: *The results of the present study suggested that preoperative plasma measurement of D-dimer concentration is not useful for predicting DVT in patients undergoing TKA.*

Keywords: *Deep vein thrombosis, Total knee arthroplasty, D-dimer*

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Total knee arthroplasty (TKA) is an extremely successful orthopedic procedure that could relieve pain, improve function, and enhance the quality of life for osteoarthritis knee. However, this procedure is also associated with a substantial risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE). In absence of thromboprophylaxis, the incidence of DVT proven by venography ranges from 40-84% after TKA[1] (61% in Phramongkutklao Hospital). With optimal thromboprophylaxis with low molecular weight heparin (LMWH), DVT occurs around 3.9-30%[1,2]. The rate of symptomatic DVT was 2.7-26 %[2,3] with 40% of such episodes manifested as proximal DVT[4], which is associated with a high risk of PE[5]. Thus, it would be helpful if patients who have higher risk of DVT, could be identified preoperatively, so more awareness and intense prophylactic regimen are adopted. The venous stasis, the injury of the vascular endothelium, and the release of tissue thromboplastin are significant in the

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development of venous thrombosis and they commonly occur during and after TKA[6-8]. Preoperative hypercoagulable state is also an interesting factor[12]. Studies have shown the correlation between preoperative plasma levels of three coagulation activation markers, which are prothrombin fragment 1 + 2, thrombin-antithrombin III complexes and D-dimer and the risk of development of DVT after elective hip or knee surgery[9,10]. Rocha[11] found three factors, fibrinogen degradation products (FDP), plasminogen activator inhibitor (PA-inhibitor), and tissue type plasminogen activator (t-PA), that were significantly associated with DVT in total hip arthroplasty (THA) and used to construct a predictive index. The predictive index, I = - 2.09 + 0.46 (FDP) + 1.39 (PA-inhibitor) - 0.24 (t-PA), was 100% sensitive and 95% specific in the prediction of DVT. Bongard[13] suggested that plasma D-dimer measurement might be useful to predict proximal DVT following major hip surgery.

D-dimer, one of the fibrin degradation products, is a protein that is produced when cross-linked fibrin is degraded by plasmin, the principal enzyme of fibrinolysis. High levels of D-dimer are found in patients, whom coagulation and fibrinolysis are co-activated, such as those with venous thromboembolism (VTE), recent trauma, or surgery and patients with severe sepsis. Many commercial assay tools and testing for D-dimer are available widely in clinical practice. These tools are frequently used to evaluate patients with clinical suspicion of VTE. The D-dimer test is based on observational studies, which show that outpatients with acute DVT and/or PE have elevated levels of D-dimer. In selected groups of such patients (low Wells' clinical probability test), a negative D-dimer test rules out VTE, obviate the need for investigations such as ultrasonography[14-16,20,21]. In the present study, the authors collected the preoperative plasma level of D-dimer in 59 patients undergoing TKA without anticoagulant prophylaxis, and correlated it with the results of postoperative venography.

Material and Method

The present study was the part of the prevalence of thrombophilia and venous thromboembolism in TKA without thromboprophylaxis study at Phramongkutklao hospital between October 1, 2002 and May 31, 2004 by Suwat R, et al. The authors prospectively enrolled consecutive eligible patients undergoing TKA. The exclusion criteria were recent trauma, bleeding, myocardial infarction, stroke, acute infection, and venous thromboembolic disease. Moreover, patients who were diagnosed with congenital or acquired haemostatic disorders, rheumatoid arthritis, renal impairment, inflammatory bowel disease, and metastatic cancer were also excluded along with patients who were using drugs interfering with hemostasis and have allergic to contrast media and serum creatinine > 2 mg%. Informed consent was obtained.

D-dimer was determined by a commercial latex agglutination immunoassay test (Fibrinosticon, BioMerieux) (Fig. 1) in a semi-quantitative technique at 2 weeks before surgery. Laboratory test was performed by one technician.

All TKAs were done by one highly experienced surgeon and no postoperative anticoagulant prophylaxis was prescribed.

The incidence of DVT was evaluated by mandatory bilateral ascending venography in all cases at the 6^{th}-10^{th} postoperative day or earlier if clinical symptoms occurred.

Then four indexes, sensitivity, specificity, positive, and negative predictive values, were calculated.

Results

Of the 59 patients that were recruited in this study, 53 patients (89%) were women. The patients' mean age, weight, and height was 69.5 years (range 60-79), 57.2 kg (range 50-65), and 154.6 cm (range 145-165) respectively. There were no patients who had evidence of co-morbid conditions affecting D-dimer levels. The preoperative diagnosis was osteoarthritis

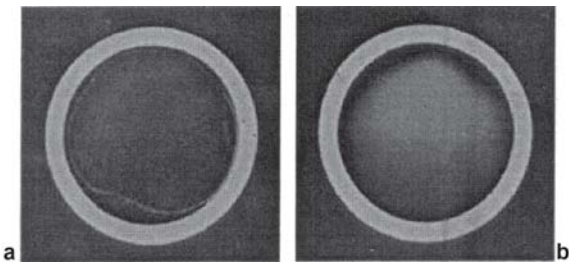

Fig. 1 D-dimer test (*Fibrinosticon*) a. positive, b. negative

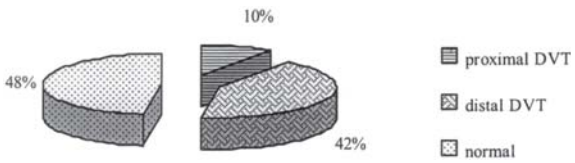

Fig. 2 Percentage of DVT in 59 patients after TKA

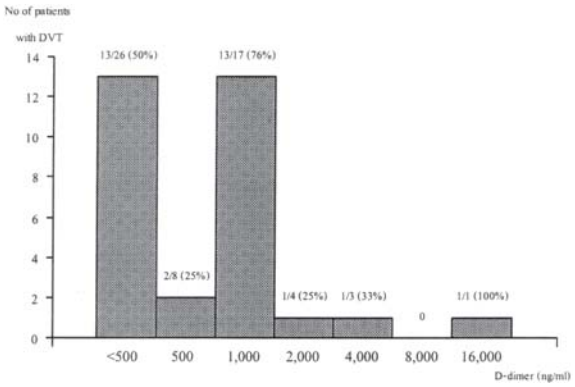

Fig. 3 Thrombosis incidences by strata of preoperative D-dimer plasma level. The percentages of patients with positive venography were given over each histogram

knee in 56 (95%) patients and aseptic loosening in three (5%).

Thirty-one of fifty-nine patients (52.5%) developed DVT, 6 proximal (10.2%) and 25 distal (42.4%). Neither episodes of confirmed pulmonary embolism nor deaths were observed.

Thrombosis incidence for each distribution of D-dimer plasma levels are reported in the Fig. 3. At the cutoff of 500 ng/ml (D-dimer < 500 ng/ml, the test was considered negative, and D-dimer 500 ng/ml or more, the test was considered positive), the correlation of preoperative D-dimer and postoperative DVT is shown in Table 1. The sensitivity, specificity, positive and negative predictive values of the preoperative D-dimer concentration for the development of subsequent DVT were 58%, 46%, 55%, and 50% respectively. The sensitivity, specificity, positive and negative predictive values calculated at cutoff points 500, 1,000, and 2,000 ng/ml are presented in Table 2.

Discussion

In patients who are considered clinically unlikely to have DVT and have a negative D-dimer test, the diagnosis of DVT is safe to excluded without the need for further diagnostic testing[17,18]. However, whether an elevated level of D-dimer before major surgery is associated with the occurrence of post-operative DVT has not been definitely established and warrants further investigation.

This study shows that the preoperative plasma levels of D-dimer have a low sensitivity, low specificity, and low positive and negative predictive values. At the cutoff of 500 ng/ml, the sensitivity, specificity, positive and negative predictive values were 58%, 46%, 55%, and 50% respectively.

The limit of detection at 500 ng/ml of the semi-quantitative latex agglutination D-dimer test (*Fibrinosticon*) might lower the sensitivity for prediction. Cofrancesco[9] investigated in elective hip surgery and found correlation between preoperative plasma level of D-dimer and the risk of DVT after the operation, but their cutoff point was 60 ng/ml. At this cutoff point, the sensitivity, specificity, positive and negative predictive values were 76%, 40%, 47%, and 71%, respectively. Bongard[13] suggested that plasma D-dimer measurement might be useful to predict proximal DVT following major hip surgery. At a cutoff of 500 ng/ml, as determined by ROC curve analysis, the sensitivity, specificity, positive and negative predictive values of the preoperative D-dimer

Table 1. Correlation of preoperative D-dimer and postoperative DVT at the cutoff value 500 ng/ml

	DVT	No DVT	
Test positive: D-dimer 500 ng/ml or more	18	15	n = 33
Test negative: D-dimer < 500 ng/ml	13	13	n = 26
	n = 31	n = 28	

Table 2. Performances of preoperative D-dimer plasma levels in predicting postoperative deep vein thrombosis

D-dimer (ng/ml)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Cutoff: 500	58%	46%	55%	50%
Cutoff: 1,000	51%	68%	64%	56%
Cutoff: 2,000	10%	82%	38%	45%

concentration for the development of subsequent proximal DVT were 93%, 23%, 36% and 96% respectively. Although the same cutoff point as our study was used, the difference of the sensitivity, specificity, positive and negative predictive values might be due to the different procedures.

Our result is similar to study of Bounameaux[19] that suggested plasma measurements of D-dimer concentration is not a value for predicting DVT in patients undergoing TKA. D-dimer plasma concentrations were not different between patients who developed DVT and those who did not. In addition, the receiver operating characteristics curve analysis did not provide any useful cutoff values that would allow the individual diagnoses to be made.

D-dimer level may be useful when combined with some clinical features like in an approach for acute DVT. Further studies are needed.

Conclusion

The results of this study suggested that preoperative plasma measurements of D-dimer concentration were not useful for predicting DVT in patients undergoing TKA.

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การตรวจค่า D-dimer ในเลือดก่อนผ่าตัดเปลี่ยนข้อเข่าเทียม เพื่อทำนายภาวะลิ่มเลือดอุดตันในหลอดเลือดดำที่เกิดตามหลังการผ่าตัด

ธไนนิธย์ โชตนภูติ, ดนัย หีบท่าไม้, วรสัณห์ ทวีวุฒิทรัพย์, สาธิต เที่ยงวิทยาพร, สุวัฒน์ รสจันทร, กฤษณ์ กาญจนฤกษ์

***ภูมิหลัง**: ภาวะลิ่มเลือดอุดตันในหลอดเลือดดำ (deep vein thrombosis) ยังคงเป็นภาวะแทรกซ้อนที่สำคัญภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมแม้ว่าจะให้การป้องกันแล้วก็ตาม ถ้าหากสามารถจำแนกได้ว่าผู้ป่วยรายใดมีความเสี่ยงสูงในการเกิดภาวะลิ่มเลือดอุดตันก็จะเป็นประโยชน์อย่างมาก เพื่อช่วยเฝ้าระวังและให้การป้องกันที่เข้มข้นมากยิ่งขึ้นการที่มีค่าของ D-dimer ในเลือดปกติร่วมกับ low clinical probability สามารถช่วย rule out ภาวะลิ่มเลือดอุดตันในหลอดเลือดดำแบบเฉียบพลันได้ และ D-dimer ยังเป็นหนึ่งใน coagulation activation marker ที่มีหลายการศึกษาพยายามนำไปใช้ในการทำนายภาวะลิ่มเลือดอุดตันในหลอดเลือดดำที่เกิดหลังการผ่าตัดข้อสะโพกหรือข้อเข่า การศึกษานี้ได้ทำขึ้นเพื่อหาความสัมพันธ์ระหว่างค่า D-dimer ในเลือดก่อนผ่าตัดกับการเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำหลังผ่าตัดเปลี่ยนข้อเข่าเทียม*

***วัตถุประสงค์**: เพื่อประเมินว่าค่า D-dimer ในเลือดก่อนผ่าตัด 2 สัปดาห์ สามารถนำมาใช้ทำนายโอกาสเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำหลังทำผ่าตัดเปลี่ยนข้อเข่าเทียมได้หรือไม่*

***วัสดุและวิธีการ**: เก็บเลือดของผู้ป่วยเพื่อตรวจค่า D-dimer ก่อนที่ผู้ป่วยจะเข้ารับการผ่าตัดเปลี่ยนข้อเข้าเทียม 2 สัปดาห์ และส่งตรวจ bilateral ascending contrast venography เพื่อตรวจหาภาวะลิ่มเลือดอุดตันในหลอดเลือดดำประมาณวันที่ 6 ถึง 10 หลังการผ่าตัดหรือก่อนหน้านั้นถ้าผู้ป่วยมีอาการ*

***ผลการศึกษา**: ผู้ป่วยจำนวน 59 คนถูกเก็บเลือดเพื่อตรวจหาค่า D-dimer ก่อนได้รับการผ่าตัดเปลี่ยนข้อเข่าเทียม หลังผ่าตัดพบภาวะลิ่มเลือดอุดตันในหลอดเลือดดำในผู้ป่วย 31 ราย (53%) จากการตรวจด้วย venography หากใช้ค่า D-dimer ที่ 500 ng/ml เป็นสิ่งตัดสิน โดยถ้าค่า D-dimer น้อยกว่า 500 ng/ml ถือเป็น test negative และถ้าค่ามากกว่าหรือเท่ากับ 500 ng/ml ถือเป็น test positive จะคำนวณได้ค่า sensitivity 58%, specificity 46%, positive predictive value 55% และ negative predictive value 50%*

***สรุป**: ผลที่ได้จากการศึกษานี้บ่งบอก D-dimer ในเลือดของผู้ป่วยก่อนเข้ารับการผ่าตัดเปลี่ยนข้อเข่าเทียมไม่สามารถนำมาใช้ในการทำนายโอกาสเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำหลังผ่าตัดได้*