The Prevalence of Thrombophilia and Venous Thromboembolism in Total Knee Arthroplasty

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Background: *Venous thromboembolism (VTE) is a common and potential serious complication in lower extremity surgeries, especially in hip and knee arthroplasty. Pulmonary embolism is one of the most fatal complications. The recognition of VTE in the lower limb has been considered as an indication for anticoagulation. Many studies have shown that thrombophilia is one factor of VTE and the most common causes are protein C, protein S and antithrombin III deficiency, factor V leiden and dysfibrinogenemia. VTE is a disease of Western populations because of well documentation of incidence and many studies about thrombophilia. In Thailand, the prevalence of VTE has been unclear.*
Objective: *The present prospective study evaluated the prevalence of thrombophilia and venous thromboembolism after total knee arthroplasty in patients who did not receive prophylactic treatment of VTE in Phramongkutklao Hospital.*
Study design: *Descriptive prospective consecutive case studies.*
Setting: *The Department of Orthopedic Surgery, Phramongkutklao Hospital, Bangkok Thailand.*
Material and Method: *Blood sample was examined at 2-3 weeks before TKA for measuring the level of thrombophilia. Bilateral ascending contrast venography of the lower extremities was performed routinely between 6^{th}-10^{th} post operative days after total knee arthroplasty.*
Results: *The authors studied 100 patients, 94 primary TKA and 6 revisions TKA. Sixty-one (61%) were positive for deep vein thrombosis. Eleven patients with positive venograms showed bilateral DVT, twelve (12%) had a proximal DVT, one was protein C deficiency, nine were protein S deficiency, 18 were antithrombin III deficiency, and 36 were positive study for FDP(D-dimer), However, no one was found with factor V leiden. Odds ratio of protein S deficiency was 0.9506, Antithrombin III deficiency was 0.7376, and FDP(D-dimer) was 1.229. The protein C deficiency and factor V leiden was undetermined.*
Conclusion: *Patients who have total knee arthroplasty performed are at high risk for deep venous thrombosis. Although fetal pulmonary embolism rarely occurs in Thai populations, mechanical prevention was routinely used and prophylactic regimen should be a part of management of patients who undergo total knee arthroplasty.*

Keywords: *Thrombophilia, Venous thromboembolism, Total knee arthroplasty*

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Venous thromboembolism (VTE) is a common and potential serious complication of lower extremity surgery, especially in hip and knee arthroplasty. Several studies have shown the prevalence of deep venous thrombosis after total knee arthroplasty (TKA) about 40-88%[1-8]. While the prevalence of proximal thrombi is between 5-20%[2,3,9], 20% of calf thrombi may extend to the proximal deep vein[10-12] and 40-50% risk pulmonary embolism (PE). Pulmonary embolism is one of the most fatal complications and approximately 90% arise from proximal deep vein thrombosis of the lower extremities.

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The formation of deep vein thrombosis (DVT) is multifactor and best described by Virchow[13] in 1859: "Virchow triad" 1) hypercoagulability or thrombophilia, 2) endothelial injury, and 3) venous stasis. The most common causes of thrombophilia are protein C or protein S and anthithrombin III deficiency, factor V Leiden, and dysfibrinogenemia[14]. When TKA is performed, it produces a release of thromboplastin that activates the clotting cascade. Surgery leads to endothelial injury and venous stasis caused by two mechanisms that the use of tourniquet and post operative immobilization, which inhibits normal venous return. For these reasons, total knee arthroplasty is at high risk for deep venous thrombosis.

Almost all of the cases that have a thrombi were clinically asymptomatic and cannot be diagnosed by physical examination. It can cause fatal pulmonary embolism (PE) or develop late complication such as post thrombotic syndrome (PTS) in about 46-58%[15,16] of patients.

In Thailand, the authors do not have an exact prevalence of thrombophilia. Furthermore, there was no prevalence of DVT in patients who had TKA performed and who did not receive the thromboprophylaxis agent. The present study evaluated the prevalence and correlation of thrombophilia and DVT after total knee arthroplasty in patients who did not receive prophylaxis thrombophelic agent in Phramongkutklao Hospital.

Material and Method

All consecutive patients who underwent total knee arthroplasty (TKA) in the orthopedic department of Phramongkutklao Hospital and who signed informed consent were included in the present prospective case study that ran from October 2002 to May 2004. Patients who had a history of VTE, hematological disease, congestive heart failure (CHF), malignancy, varicose vein, and oral contraceptive drug were excluded from blood examination for thrombophilic factors. Furthermore, the patients who had a history of iodine allergy, hypercoagulability disease, oral anticoagulant use, chronic liver disease, serum creatinine more than 140 mmoL/L, and could not be injected with radio-contrast material into superficial the vein of the dorsum of both feet were excluded from the study. One hundred patients (18 males and 82 females) had routine contrast venography of the lower extremities between the 6^{th}-10^{th} post operative days after cemented total knee arthroplasty. The average age was 69.4 years old (43-80 years old). Blood samples were examined for protein C, protein S, antithrombin III, factor V Leiden, and FDP (D-dimer) 2-3 weeks before surgery.

The authors used Odd ratio to determine the association between thrombophilic factors and DVT after TKA.

The diagnosis of patients who underwent TKA is shown in Table 1. The authors collected data on the number of positive venograms and the location of the DVT that were reviewed by a vascular radiologist.

Results

The authors studied 100 total knee arthroplasty (TKA). Primary TKA was performed in 94 knees from osteoarthritis and six revisions from aseptic loosening. Sixty-one venograms (61%) were positive for deep vein thrombosis, and 11 showed bilateral DVT. Twelve patients had thrombi in proximal deep vein. There was no isolate contralateral thrombosis. Symptomatic pulmonary embolism was found in one patient (1%) and confirmed by positive perfusion lung scan. She had bilateral deep femoral vein thrombosis. One patient had protein C deficiency, nine had protein S deficiency, 18 had antithrombin III deficiency, and 36 were positive for FDP (D-dimer). No one was found with factor V leiden in the blood. In the primary TKA group, the venogram was positive in 52 patients (55.3%, 52/94) and in 4 patients (66.7%, 416) in the revision group. The locations of the thrombi are shown in Table 3 and 4.

Most thrombi were found in calf vein (82.1%). The posterior tibial vein is the most common, occurring in about 28.4%, and the posterior tibial combined peroneal vein was the second, and was found in about 19.4% of the patients. The proximal deep vein into popliteal, femoral, or common iliac vein was found in 17.9% of patients (Table 4). Women had higher positive and frequency when compared to male at 65.6% (48/73) in females and 44.4% (8/18) in males (Table 2). Odds ratio of protein S deficiency was 0.9506, antithrombin III deficiency was 0.7376, and FDP(D-dimer) was 1.229. Protein C deficiency and factor V leiden were undetermined.

Discussion

The present study showed a high prevalence of deep venous thrombosis about 61% after total knee arthroplasty in patients without thromboprophylaxis. The authors found the prevalence of protein C deficiency (1%), protein S deficiency (9%), and antithrombin III deficiency (18%) to be quite high when com-

pared with western studies[17]. This may be due to the older age of the cases in the present study and related with acquired thrombophelia. Although in the West, factor V leiden is related to VTE, in this study it was not. Protein S and antithrombin III deficiency reduce fibrinolytic activity and put the patients at increased risk of VTE. The prevalence of FDP (D-dimer) is high and positive in blood at both preoperative and postoperative, in cases positive for venogram.

The prevalence of proximal thrombi was similar to other studies[2,3,9]. Stulberg BN, Insall JN et al[2] studied post operative venogram and perfusion lung scan in 317 patients. Pulmonary embolism was diagnosed clinically in 1.7%, and 7% had positive perfusion lung scan. Hass SB et al[4] studied the incidence of DVT after TKA, and found that 10% had asymptomatic pulmonary embolism. In other studies asymptomatic pulmonary embolism was found in 5-20%, symptomatic 1-10%, and fatal pulmonary embolism in about 0.25-0.7%[4,5,8,25,26]. In the present study, one patient (1.1%) had symptomatic pulmonary embolism, confirmed by positive lung scan, and she had a positive venogram on both deep femoral veins. However, the correlation between proximal thrombi and pulmonary embolism could not be evaluated because there is only one case. The authors did not evaluate the incidence of asymptomatic pulmonary embolism because the authors did not routinely perform postoperative perfusion lung scan. However, in the present study, all cases of calf thrombi did not develop symptomatic pulmonary embolism.

In the four cases that had two stages of bilateral total knee arthroplasty, all four cases had distal DVT in the first total knee arthroplasty and received anticoagulant. The authors did not find DVT in the first leg after performing postoperative venography in the second total knee arthroplasty.

In the present study, venography is the gold standard. However, it is an invasive technique for detecting DVT rather than the use of duplex ultrasound that is less sensitive, inaccurate and requires a well-experienced radiologist[6-8] for detecting asymptomatic DVT in calf vein. Although it is a noninvasive technique, the authors think that thromboprophylaxis will be a part of the management of total knee arthroplasty in the future for patients in Thailand. To reduce unnecessary anticoagulant prophylaxis and avoid invasive investigation such as venography in patients who do not have DVT, the authors, in a future study, will examine the risk factor that increases the risk of DVT

Table 1. Diagnosis of patients

Diagnosis	Right	Left	Total
Osteoarthritis	56	38	94
Aseptic loosening	3	3	6
Total	59	41	100

Table 2. Number of positive venography

Sex/Result	Positive	Negative	Total
Male	8	10	18 (19.8 %)
Female	48	25	73 (80.2 %)
Total	56 (61.5 %)	35 (38.5 %)	91

Table 3. The location of thrombi after TKA

Location	No.
Distal	
Muscular and collateral	2
Anterior tibia	4
Posterior tibia	19
Peroneal	6
Anterior and posterior tibia	4
Anterior tibia and peroneal	3
Posterior tibia and peroneal	13
Anterior and posterior tibia and peroneal	4
Total	55 (82.1 %)
Proximal	
Popliteal	9
Deep femoral or common iliac	3
Total proximal	12 (17.9 %)
Total proximal and distal	67

Table 4. The location of bilateral thrombosis

Distal/Distal	Proximal/Distal	Proximal/Proximal	Distal/Proximal	Total
9	1	1	0	11

(Ipsilateral / Contralateral that performed TKA)

in a Thai population, and will search the other markers instead of using venography, that represent patients who have DVT.

References

1. Clagett GP, Anderson FA Jr, Geerts W, Heit JA, Knudson M, Lieberman JR, et al. Prevention of venous thromboembolism. Chest 1998; 114(5 Suppl): 531S-60S.
2. Stulberg BN, Insall JN, Williams GW, Ghelman B. Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. J Bone Joint Surg Am 1984; 66: 194-201.
3. McKenna R, Bachmann F, Kaushal SP, Galante JO. Thromboembolic disease in patients undergoing total knee replacement. J Bone Joint Surg Am 1976; 58: 928-32.
4. Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Am 1990; 72: 27-31.
5. Kim YH, Kim JS. Incidence and natural history of deep-vein thrombosis after total knee arthroplasty. A prospective, randomised study. J Bone Joint Surg Br 2002; 84: 566-70.
6. Oishi CS, Grady-Benson JC, Otis SM, Colwell CW Jr, Walker RH. The clinical course of distal deep venous thrombosis after total hip and total knee arthroplasty, as determined with duplex ultrasonography. J Bone Joint Surg Am 1994; 76: 1658-63.
7. Ciccone WJ, Fox PS, Neumyer M, Rubens D, Parrish WM, Pellegrini VD Jr. Ultrasound surveillance for asymptomatic deep venous thrombosis after total joint replacement. J Bone Joint Surg Am 1998; 80: 1167-74.
8. Cohen SH, Ehrlich GE, Kauffman MS, Cope C. Thrombophlebitis following knee surgery. J Bone Joint Surg Am 1973; 55: 106-12.
9. Lotke PA, Ecker ML, Alavi A, Berkowitz H. Indications for the treatment of deep venous thrombosis following total knee replacement. J Bone Joint Surg Am 1984; 66: 202-8.
10. Grady-Benson JC, Oishi CS, Hanson PB, Colwell CW Jr, Otis SM, Walker RH. Postoperative surveillance for deep venous thrombosis with duplex ultrasonography after total knee arthroplasty. J Bone Joint Surg Am 1994; 76: 1649-57.
11. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. Lancet 1969; 2: 230-2.
12. Zilliacus H. On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with a particular reference to the post thrombotic sequelae. Acta Med Scand Suppl 1946; 171: 1-221.
13. Virchaw R. Never fall van todlicker emboli der. kungeranteries. Arch Path Anat 1859; 10: 225.
14. Heijboer H, Brandjes DP, Buller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med 1990; 323: 1512-6.
15. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 2002; 162: 1144-8.
16. Caprini JA. Investigating the prevalence and pathophysiology of the post-thrombotic syndrome after total hip arthoplasty. In: 13th Annual Congress of the American College of Phlebology. November 11-13, 1999. Scottsdale, Arizona.
17. Gladson CL, Scharrer I, Hach V, Beck KH, Griffin JH. The frequency of type I heterozygous protein S and protein C deficiency in 141 unrelated young patients with venous thrombosis. Thromb Haemost 1988; 59: 18-22.
18. Talalak P. Thromboembolism in Thailand: incidence, coagulogram and its significance in therapeutic implication and prognosis. J Med Assoc Thai 1976; 59: 6-11.
19. Vathesatogkit P, Saenghirunvattana S, Nitiyanant P. Autopsy proven cases of pulmonary thromboembolism: 18-year study at Ramathibodi Hospital. J Med Assoc Thai 1989; 72: 271-4.
20. Atichartakarn V, Songsiridej N, Jootar S. Incidence and risk factors of deep vein thrombosis among Thai patients - their implications on patients' management. J Med Assoc Thai 1988; 71: 231-7.
21. Phornphibulaya P, Buranapong P, Ruksawin N, Viranuvatti J. The incidence of postoperative deep vein thrombosis in Thais. J Med Assoc Thai 1984; 67: 377-81.
22. Westrich GH, Allen ML, Tarantino SJ, Ghelman B, Schneider R, Laskin RS, et al. Ultrasound screening for deep venous thrombosis after total knee arthroplasty. 2-year reassessment. Clin Orthop Relat Res 1998; 356: 125-33.
23. Westrich GH, Scheider R, Compression between color doppler imaging and venography in detection of Deep vein thrombosis follow total joint arthroplasty. Contemp Surg 1997; 51: 225-34.

24. Garino JP, Lotke PA, Kitziger KJ, Steinberg ME. Deep venous thrombosis after total joint arthroplasty. The role of compression ultrasonography and the importance of the experience of the technician. J Bone Joint Surg Am 1996; 78: 1359-65.
25. Khaw FM, Moran CG, Pinder IM, Smith SR. The incidence of fatal pulmonary embolism after knee replacement with no prophylactic anticoagulation. J Bone Joint Surg Br 1993; 75: 940-1.
26. Ansari S, Warwick D, Ackroyd CE, Newman JH. Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. J Arthroplasty 1997; 12: 599-602.

ความชุกของภาวะการแข็งตัวของเลือดและภาวะการเกิดลิ่มเลือดแข็งตัวในหลอดเลือดดำ ในการผ่าตัดข้อเข่าเทียม

ธไนนิธย์ โชตนภูติ, พิพัฒน์ องค์น้ำทิพย์, สุวัฒน์ รสจันทร์, สุธี ชิวพิพัฒน์, ตระกูล ฟูเจริญยศ, อนุชิต เริ่มธารทอง

ภูมิหลัง: *ภาวะการแข็งตัวของเลือด และภาวะการเกิดลิ่มเลือดแข็งตัวในหลอดเลือดดำ เป็นภาวะแทรกซ้อนที่รุนแรงและพบได้บ่อยในการผ่าตัดของระยางค์ส่วนล่าง โดยเฉพาะการผ่าตัดเปลี่ยนข้อเทียมของเข่าและสะโพกซึ่งอาจจะลุกลามเปลี่ยนเป็นภาวะลิ่มเลือดอุดตันภายในปอดซึ่งภาวะนี้รุนแรงถึงเสียชีวิตได้ ความสำคัญและคำนึงถึงภาวะเหล่านี้เป็นเหตุให้มีการพิจารณาให้ยาต่อต้านการแข็งตัวของเลือดในการผ่าตัดข้อเข่าเทียม หลาย ๆ การศึกษาแสดงให้เห็นว่าภาวะการแข็งตัวของเลือด เป็นปัจจัยหนึ่งของการเกิดลิ่มเลือดแข็งตัวในหลอดเลือดดำ สาเหตุจากการขาด protein C, protein S, และ antithrombin III, การมี factor V Leiden, และ ภาวะ dysfibrinogenemia มีการศึกษาของโรคนี้มากในชาวตะวันตกจนเกิดมีแนวทางในการให้ยาป้องกันการแข็งตัวของเลือด ส่วนในชาวตะวันออกโดยเฉพาะในประเทศไทย ความชุกของโรคนี้ยังไม่มีการศึกษาและรายงานเป็นที่แน่นอน*

วัตถุประสงค์: *เป็นการประเมินความชุกของการเกิดลิ่มเลือดแข็งตัวในหลอดเลือดดำ และภาวะการแข็งตัวของเลือดหลังการผ่าตัดข้อเข่าเทียมในผู้ป่วยที่ไม่เคยได้รับยาป้องกันการแข็งตัวของเลือดในโรงพยาบาลพระมงกุฎเกล้า*

การออกแบบการศึกษา: *เป็นการศึกษาไปข้างหน้า*

วัสดุและวิธีการ: *เป็นการศึกษาในผู้ป่วยที่ได้รับการผ่าตัดข้อเข่าเทียมจำนวน 100 ราย โดยเก็บตัวอย่างเลือดก่อนการผ่าตัด 2-3 สัปดาห์ เพื่อวัดระดับของการแข็งตัวของเลือดหลังจากการผ่าตัดข้อเข่าเทียมแล้วประมาณ 6-10 วัน ผู้ป่วยจะได้รับการฉีดสารทึบแสงทางรังสีเข้าทางหลอดเลือดของขาทั้งสองข้างเพื่อประเมินภาวะการอุดตันของหลอดเลือดดำ*

ผลการศึกษา: *ผู้ป่วยทั้งหมด 100 ราย จำแนกเป็นการผ่าตัดเข่าปกติจำนวน 94 ราย และผ่าตัดซ้ำในผู้ที่เคยผ่าตัดมาแล้วจำนวน 6 ราย พบว่า 61 ราย (61%) เกิดภาวะหลอดเลือดดำอุดตัน พบ 11 รายเกิดภาวะหลอดเลือดดำอุดตันของขาทั้งสองข้าง มีผู้ป่วย 12 รายที่เป็นการอุดตันของเส้นเลือดส่วนต้น, ทางด้านภาวะการแข็งตัวของเลือด พบภาวะ protein C deficiency 1 ราย, protein S deficiency 9 ราย, antithrombin III deficiency 18 ราย, พบภาวะ FDP (D-dimer) 36 ราย, และไม่พบภาวะ factor V Leiden เลย Odds ratio ของ protein S deficiency 0.9506, antithrombin III deficiency 0.7376, FDP (D-dimer) 1.229 ส่วน Odds ratio ของ protein C deficiency และ factor V Leiden ไม่สามารถวัดได้*

สรุป: *ผู้ที่ได้รับการผ่าตัดข้อเข่าเทียมถือได้ว่าเป็นผู้ที่เสี่ยงต่อภาวะหลอดเลือดดำอุดตัน แม้นว่าภาวะลิ่มเลือดอุดตันภายในปอดจะพบน้อยมากก็ตาม การป้องกันภาวะแทรกซ้อนเหล่านี้โดยกลศาสตร์ควรทำอย่างสม่ำเสมอและควรพิจารณาการใช้ยาป้องกันการแข็งตัวของเลือดร่วมด้วยในผู้ที่ได้รับการผ่าตัดข้อเข่าเทียม*