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PPREOPERATIVE D-DIMER AND DEEP VEIN THROMBOSIS IN PATIENTS SCHEDULED FOR ORTHOPEDIC SURGERY

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ABSTRACT

Background: The present study was performed to obtain cut-off value of D-dimer for negative DVT in patients scheduled for spine, joint, or fracture surgery retrospectively. **Methods:** Data of the patients who received spine (1820 cases), fracture (246 cases), and joint (516 cases) surgeries in these 5 years were extracted. In patients with D-dimer ≧ 2.0 μg/mL, echography was performed to detect thrombosis in heart, neck, and lower extremities. Patients were divided into three subgroups with no thrombus, new thrombus, or old thrombus by echography. Cut-off value was calculated using receiver operatorating characteristic curve. **Results:** In spine surgery, D-dimer was significantly higher in the order of new thrombus > old thrombus > no thrombus. Using the cut-off values obtained in this study, 6 cases with new thrombus and 25 cases with old thrombus in spine surgery, 19 cases with new thrombus and 36 cases with old thrombus in fracture surgery, and 4 cases with new thrombus and 2 cases with old thrombus in joint surgery were false negatives. The minimum D-dimer with thrombus was 2.0 μg/mL, 2.1 μg/mL, and 2.0 μg/mL, in spine, fracture, and joint surgery, respectively. **Conclusions*:*** Echography should be performed to detect DVT when preoperative D-dimer is ≧ 2.0 μg/mL in spine surgery, ≧ 2.1 μg/mL in fracture surgery and ≧ 2.0 μg/mL in joint surgery.

KEYWORDS: D-dimer, Deep vein thrombosis, Spine surgery, Fracture surgery, Joint replacement surgery.

INTRODUCTION

Pulmonary embolism (PE) is one of the perioperative critical complications. Deep vein thrombosis (DVT) might induce PE. Therefore, screening DVT before surgery is very important. To detect DVT, angiography or contrast enhanced computed tomography should be used. However, they were invasive, spent much cost and time, and some patients have a risk for allergic reaction. Echography is also useful[1] and non-invasive, but still time-consuming. Many clinical scores to suspect DVT with or without D-dimer value[2] were investigated. However, they all remains controversial. There are many studies to investigate usefulness of D-dimer to suspect DVT, especially after surgery.[3,4] D-dimer increases not only in DVT but also in various diseases and conditions, including tumors, aging, infections, and surgery.[5] Therefore, the usefulness of D-dimer to suspect DVT might be different according to patient's condition, and it is difficult to suspect DVT using D-dimer after surgery. To prevent postoperative PE, preoperative diagnosis of DVT is quite important as well as postoperative diagnosis. However, we could not find any studies of preoperative diagnosis of DVT.

We have measured D-dimer routinely as preoperative laboratory test in all patients for surgery using AQT test™ (Radiometer, Copenhagen, Sweden) in our hospital. When D-dimer is ≧ 2 μg/mL, echography of heart, neck and lower extremities is performed to detect thrombus.

The present study was performed to obtain cut-off value of D-dimer for negative DVT preoperatively in patients scheduled for spine, joint, or fracture surgery, retrospectively using the date of patient's records operated in these 5 years in our hospital.

MATERIALS AND METHODS

A retrospective study was conducted after the approval of the Ethics Committee of the hospital. Data of the patients who received spine (1820 cases), fracture (246 cases), and joint (516 cases) surgeries in recent 5 years were extracted. Informed consent to use data for publication were obtained with consent for anesthesia from all patients.

According to our usual preoperative protocol, D-dimer was measured preoperatively in all patients scheduled for surgery. When D-dimer was ≧ 2 μg/mL, echography was

performed to detect thrombosis in heart, neck, and lower extremities. D-dimer was measured with the D-dimer AQT test™ (Radiometer, Copenhagen, Sweden). Patients were divided into three subgroups with no thrombus, new thrombus, or old thrombus by echography. Cut-off value was calculated using receiver operatorating characteristic curve. Statistical analysis was performed with analysis of variance and Chi-square test for intergroup differences. A P value less than 0.05 was considered to be statistically significant.

RESULTS

The number of patients whose preoperative D-dimer ≧ 2 μg/mL was 205 in spine, 127 in fracture, and 41 in joint surgeries. In fracture surgery, patients with new thrombus and old thrombus were significantly older than those with no thrombus and patients with D-dimer < 2 μg/mL (Table 1). No other demographic data had significant differences among the groups.

In spine surgery, D-dimer with new thrombus and old thrombus were significantly higher than those with no thrombus, and D-dimer with new thrombus was significantly higher than that with old thrombus (Table 2). If these cut-off values in the Table 2 were used, 6 cases with new thrombus and 25 cases with old thrombus in spine surgery, 19 cases with new thrombus and 36 cases with old thrombus in fracture surgery, and 4 cases with new thrombus and 2 cases with old thrombus in joint surgery were false negative.

No patients showed clinical symptom of pulmonary embolism or DVT during hospitalization.

Table 1: Demographic data.

Surgery	**Spine**				**Fracture**				**Joint**			
D-dimer (μ/mL)	< 2	≧2	≧2	≧2	< 2	≧2	≧2	≧2	< 2	≧2	≧2	≧2
Thrombus		No	New	Old		No	New	Old		No	New	Old
Age years）	75±5	74±5	74±6	74±6	77±15	76±14	84±11*	83±8*	73±11	74±8	78±3	75±10
Male／Female	319/1296	28/98	3/15	18/43	23/96	9/31	2/24	11/50	86/389	3/12	0/6	4/16
Height (cm）	159±23	157±6	156±5	157±28	157±6	156±11	148±9	151±9	158±24	153±9	153±5	151±5
Body weight (kg）	60±7	61±7	59±6	55±12	61±7	55±14	47±10*	49±10	59±8	61±16	59±8	54±12
Number of surgery postponed	0	0	18	0	0	0	6	0	0	0	6	0

Mean ± Standard deviation or number of patients、＊: P < 0.05 vs. D-dimer < 2 and No thrombus with D-dimer ≧2 in the Fracture

Table 2: Results

Surgery	**Spine**				**Fracture**				**Joint**			
D-dimer (μ/mL)	< 2	≧2	≧2	≧2	< 2	≧2	≧2	≧2	< 2	≧2	≧2	
Thrombus		No	New	Old		No	New	Old		No	New	Old
D-dimer （μg/mL）	0.4 (0.1, 1.8)	3.2 (2.0, 19.5)	8.0 (2.6, 29.7) *,+	5.4 (2.0, 38.8) *	0.9 (0.2, 1.9)	7.0 (2.2, 37.5)	6.8 (2.1, 97.5)	7.2 (2.3, 106.6)	0.4 (0.1, 1.6)	2.9 (2, 11.1)	3.6 (1.8, 10)	2.5 (2.2, 4.4)
Cutoff value			5.1	4,8			25.9	10.7			4.5	2.3
Sensitivity			0.72	0.59			0.27	0.43			0.5	0.85
Specificity			0.86	0.83			0.95	0.7			0.93	0.44
AUC			0.79	0.67			0.54	0.51			0.6	0.44
95%CI			0.58,0.77	0.58,0.77			0.39, 0.70	0.40, 0.63			0.21, 0.94	0.23, 0.64
Minimum D-dimer with thrombus (μg/mL）			2.6	2.0			2.1	2.3			2.0	2.1

D-dimer is shown as a median (minimum, maximum). AUC: area under the curve of ROC, CI: confidence interval,
＊: P < 0,05 vs. the No thrombus in the Fracture、+: P < 0,05 vs. the Old thrombus in the Spine

DISCUSSION

In this study, only in the spine surgery, D-dimer showed significant differences in the order of new thrombus > old thrombus > no thrombus. The sensitivities were low in all groups, and if these cut-off values were used, many patients were false negative.

Some clinical scores to diagnose DVT have been investigated, [2] but they all remains controversial. Our study was a retrospective study, therefore, we could not use any scores.

We have used AQT test™ to measure D-dimer in our hospital. The cut-off value to exclude DVT is 0.5 μg/mL with AQT test™ by the manufacturer. In our previous clinical practice, we had performed echography when D-dimer was ≧ 0.5 μg/mL. However many patients for orthopedic surgery had D-dimer ≧ 0.5 μg/mL with no DVT by echography. Recently, to decrease labor and cost for echography, we have used echography when D-dimer was ≧ 2 μg/mL according to our clinical experience. Therefore, this study has a risk to miss DVT in patients with D-dimer < 2 μg/mL, though there were no patients who showed clinical symptoms of DVT or pulmonary embolism in this study.

Many devices were compared to measure D-dimer. [6] Enzyme-linked immunosorbent assay (ELISA), quantitative rapid ELISA, and advanced turbidimetric D-dimer determinations are more than 95% sensitive for DVT.[7] In another study,[8] D-dimer tests have reported sensitivities ranging from 95% to 96%, with specificities ranging from 45% to 61% and a negative predictive value ranging from 97% to 99%. [8] The D-dimer AQT test™ uses time resolved fluorescence immunoassay and when D-dimer is less than 0.5 μg/mL, DVT should be denied [9] with a sensitivity of 95%. [6] Therefore, AQT test™ is as useful as other tests.

Linkins et al. [10] suggested that a D-dimer of less than 10 μg/mL could exclude DVT in patients with low clinical score, while the cut-off values should be 5 μg/mL when patients are at moderate or high risk. Other studies showed lower D-dimer threshold. Nata et. al.[11] reported that the specificity of D-dimer for diagnosing DVT was 78.3% and its sensitivity was 93.8%, when the cut-off value was set at 3.6 μg/mL. For proximal DVT, a fixed threshold of D-dimer showing 95% sensitivity was 0.25 μg/mL.[18] Ota et al.[13] showed that when the cut-off values were set to the 95% confidence interval value of healthy volunteers as D-dimer 2.5 μg/mL, 2 patients with DVT were overlooked. By Takahashi et al.,[14] using the D-dimer threshold 1.1 μg/mL, the failure rate was 0%. D-dimer cut-off value of 0.5 μg/mL showed the specificity of 21.1% and a sensitivity of 100%.[15] Sensitivity 100% means no false-negative results. We need 100% sensitivity not to miss DVT. The sensitivity and negative predictive value for the diagnosis of DVT were reported to be 100% when using a cut-off value of 0.5 – 2.5μg/mL.[11]

The cut-off value of D-dimer should be different according to the age. Haas et al.[16] suggested a fixed cut-off value of 0.75 μg/mL for patients aged 60 years and older. In low risk patients, the cut-off value of D-dimer should be age x 0.25 μg/mL to rule out DVT. In intermediate risk patients, it should be age x 0.10 μg/mL.[15] Verma et al.[17] showed that a cut-off value should be age x 0.16 μg/mL to rule out VDT in patients older than 70 years. We did not analyze age difference because we had only small number of patients, almost old ages, and the D-dimer is useful only for ruling out DVT if results are negative, but positive results are not diagnostic because many conditions can increase D-dimer levels.[5,18] One of those is surgical procedure. Some studies investigated D-dimer after surgery. After total knee or hip replacement, there was no difference in D-dimer levels between patients with or without DVT.[4] The best cut-off level of D-dimer was 8.5 μg/mL which had 76% sensitivity, 45% specificity, and a 97% negative predictive value for the diagnosis of DVT after major lower extremity arthroplasties. [19] Okamoto et al.[3] showed that a cut-off value of D-dimer was 3.3 μg/mL on the third day after brain tumor surgery for acute and subacute DVT. However, there were false-negative cases. Therefore, they concluded 1.5 μg/mL as the cut-off value to avoid false negative.

There is no study of the cut-off values of D-dimer for diagnosis of DVT before surgery. However, patients scheduled for surgery might have some diseases to influence D-dimer, therefore, threshold of D-dimer to suspect DVT might be different from post-surgical patients and normal subjects.

The calculated cut-off values of D-dimer in this study should not be used for negative DVT because the sensitivities were not 100%. The smallest D-dimer with new DVT and old DVT were 2.6μg/mL and 2.0μg/mL in spine surgery, 2.1μg/mL and 2.3μg/mL in fracture surgery, and 2.0μg/mL and 2.1μg/mL in joint surgery, respectively, in the present study. We should use these values as cut-off values of D-dimer for negative DVT. However, we did not perform echography in patients with D-dimer less than 2 μg/mL. Therefore, the possibility of lower cut-off values than those we showed should be further investigated, even while there were not patients who showed clinical signs of DVT in all patients with D-dimer less than 2μg/m in this study.

In conclusion, echography should be used to detect DVT when preoperative D-dimer is ≧ 2 μg/mL in spine surgery, ≧ 2.1 μg/mL in fracture surgery and ≧ 2.0 μg/mL in joint surgery.

REFERENCES

1. Bernardi E, Camporese G. Diagnosis of deep-vein thrombosis. Thromb Res, 2018; 163: 201-206.
2. Kafeza M, Shalhoub J, Salooja N, Bingham L, Spagou K, Davies AH. A systematic review of clinical prediction scores for deep vein thrombosis. Phlebology, 2017; 32: 516-531.
3. Okamoto E, Ishikawa E, Kino H, Kohzuki H, Sugii N, Naito H, Hara T, Homma S, Matsuda M, Tsurubuchi T, Ishikawa T, Kawakami Y, Akutsu H. Peroperative deep vein thrombosis and D-dimer measurement in patients with brain tumor. Neurol Med Chir (Tokyo), 2022; 62: 186-194.
4. Rafee A, Herlikar D, Gilbert R, Stockwell RC, McLauchlan GJ. D-dimer in the diagnosis of deep vein thrombosis following total hip and knee replacement: a prospective study. Ann R Coll Surg Engl, 2008; 90: 123-126.
5. Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bounameaux H. D-dimer plasma concentration in various clinical conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. Thromb Res, 1993; 69: 125-130.
6. Oude Elferink RFM, Loot AE, Van de Klashorst CGJ, Hulsebos-Huygen M, Piersma-Wichers M, Oudega R. Clinical evaluation of eight different D-dimer test for the exclusion of deep venous thrombosis in primary care patients. Scand J Clin Lab Invest, 2015; 75: 230-238.
7. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V, Kalra NK. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med, 2004; 140: l9-l16.
8. Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. J Am Coll Cardiol, 2017; 70: 2411-2420.
9. Kato Y, Nishii C, Kitagawa F, Miura N, Fujita T, Ishikawa T, Ishii J. Evaluation of D-dimer assay by AQT90Flex. JJCLA, 2013; 38: 293-297.
10. Linkins LA, Bates SM, Lang E, Kahn SR, Douketis JD, Julian J, Parpia S, Gross P, Weitz JI, Spencer FA, Lee AY, O'Donnell MJ, Crowther MA, Chan HH, Lim W, Schulman S, Ginsberg JS, Kearon C. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Ann Intern Med, 2013; 15, 158: 93-100.
11. Nata S, Horomatsu S, Shintani Y, OhnoT, Akashi H, Tanaka H. D-dimer value more than 3.6 μg/ml is highly possible existance deep vein thrombosis. Kurume Med J, 2013; 60: 47-51.
12. Prochaska JH, Frank B, Nagler M, Lamparter H, Weißer G, Schulz A, Eggebrecht L, Göbel S, Arnold N, Panova-Noeva M, Hermanns I, Pinto A, Konstantinides S, Cate H, Lackner KJ, Münzel T, Espinola-Klein Ch, Wild PS. Age-related diagnostic value of D-dimer testing and the role of inflammation in patients with suspected deep vein thrombosis. Sci Rep, 2017; 7: 4591. doi: 10.1038/s41598-017-04843-x.
13. Ota S, Wada H, Nobori T, Kobayashi T, Nishio M, Nishioka Y, Noda M, Sakaguchi A, Abe Y, Nishioka J, Ishikura K, Yamada N, Nakano T. Diagnosis of deep vein thrombosis by plasma-soluble fibrin or D-dimer. Am J Hematol, 2005; 79: 274-280.
14. Takahashi, J, Shiga T, Fukuyama Y, Hoshina Y, Homma Y, Mizobe M, Numata K, Inoue T, Funakoshi H. New D-dimer threshold for Japanese patients with suspected pulmonary embolism: a retrospective cohort study. Int J Emerg Med, 2019; 28, 12: 23. doi: 10.1186/s12245-019-0242-y.
15. Gomez-Jabalera E, Montoya SB, Fuentes-Camps E, Rodriguez JRE. Age-adjusted D-dimer for the diagnosis of deep vein thrombosis. Phlebology, 2018; 33: 458-463.
16. Haas FJ, Schutgens RE, Biesma DH. An age-adapted approach for the use of D-dimers in the exclusion of deep venous thrombosis. Am J Hematol, 2009; 84: 488-491.
17. Verma N, Willeke P, Bicsán P, Lebiedz P, Pavenstädt H, Kümpers P. Age-adjusted D-dimer cut-offs to diagnose thromboembolic events: validation in an emergency department. Med Klin Intensivmed Notfmed, 2014; 109: 121-128.
18. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. Am
19. Fam Physician, 2012; 86: 913-919.
20. Sugimoto E, Kuroda T, Fujita Y, Namba Y, Mitani S. D-dimer testing cannot rule out thromboembolism after major lower extremity arthroplasties and thromboprophylaxis treatment. J Anesth, 2015; 29: 686-689.