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Original Article

Diagnostic value of the risk assessment profile for thromboembolism and plasma D-dimer level in deep vein thrombosis patients after periarticular ankle fractures

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Abstract: Objective: This study aimed to investigate the diagnostic value of the risk assessment profile for thromboembolism (RAPT) and plasma D-dimer in deep vein thrombosis (DVT) of patients with periarticular ankle fractures (PAF). Methods: A total of 85 patients who were treated due to PAF were retrospectively reviewed. After admission, patients were divided into middle to high risk group and low risk group according to the RAPT score. Results: Before surgery, DVT was found in 0 (0%) and 15 patients (22.39%) in low risk group and middle to high risk group, respectively (P<0.05). After surgery, DVT was found in 0 (0%) and 15 patients (19.44%) in low risk group and middle to high risk group, respectively (P>0.05). If 1.4 mg/L was used as a cut-off value of D dimer, the sensitivity and specificity were 87.5% and 4.3%, respectively, in the diagnosis of DVT of PAF patients. The AUC was the largest when the cut-off value of D dimer was 3.6 mg/L at which the sensitivity and specificity were 0.810 and 0.578, respectively. Conclusion: Patients with PAF have a risk for DVT in peri-operative period, with distal embolization as the major type. RAPT is associated with DVT before surgery, but not after surgery, in PAF patients. D-dimer has a low accuracy and a poor specificity in the diagnosis of DVT of PAF patients, and 3.6 mg/L is the optimal cut-off value of D-dimer in the diagnosis of DVT.

Keywords: Ankle fracture, deep vein thrombosis, risk assessment profile for thromboembolism, D-dimmer

Introduction

Deep vein thrombosis (DVT) has been a focus in studies on traumatic fracture. However, a majority of studies focus on the prevention and treatment of DVT after major orthopaedic surgery (such as hip or knee replacement and surgery for peri-hip fracture) [1, 2], and the relationship between periarticular ankle fractures (PAF) and DVT is less investigated. In this study, patients with PAF who were treated in our department between August 2014 and March 2015 were retrospectively reviewed, and the role of the risk assessment profile for thromboembolism (RAPT) and D-dimer (DD) in the diagnosis of DVT was explored, aiming to improve the management of DVT in PAF patients.

Materials and methods

General information

Inclusion criteria: 1) patients were diagnosed with PAF (ankle fracture and Pilon fracture); 2) Patients were older than 16 years; 3) the time from injury to surgery was shorter than 3 weeks (fresh fracture). Exclusion criteria: 1) patients had incomplete medical record; 2) patients were younger than 16 years; 3) patients were diagnosed with old fracture; 4) patients had multiple fractures; 5) patients received anticoagulation therapy before injury; 6) patients had open wound.

A total of 85 patients with PAF received surgical interventions in our department between

Table 1. Incidence of DVT according to etiology and type of ankle fracture

Characteristics	Thrombosis	Non-thrombosis	P	F/X^2
Etiology				
High energy	8	4	-	-
Non-high energy	13	60	0.010	10.730
Type of ankle fracture				
Singl	1	3		
Double	8	24		
Triple	8	33		
Pilon	5	3	0.090	6.470
AO classification				
Type A	3	9		
Type B	12	35		
Type C	6	20	0.973	0.055

August 2014 and March 2015. Informed consent was obtained before study and this study was approved by the Ethics Committee of our hospital. The median age of these patients was 44.0 years (range: 16-79 years). There were 51 males (60%) and 34 females (40%). Single ankle fracture was found in 4 patients (4.70%), double ankle fracture in 32 (37.65%), triple ankle fracture in 41 (48.24%), and Pilon fracture in 8 (9.41%). In addition, high energy injury was found in 12 patients and low energy injury in 73. According to the AO classification system, type A fracture was found in 12 patients, type B in 47 and type C in 26.

Methods

After admission, routine management was conducted, and RAPT scoring was performed in these patients. 2 days after admission, 1 day before surgery, and 1, 3 and 5 days after surgery, routine blood test and coagulation function detection were conducted.2 days after admission and 3 days after surgery, bilateral lower limb ultrasound examination was performed (the median time from fracture to ultrasound examination was 3.78 days [range: 2-14 days]). After surgery, RAPT scoring was performed again. According to the RAPT score, patients were divided into low risk group (0-5 point) and middle to high risk group (>5 point). For patients with RAPT score >5, physical prophylaxis of DVT was employed. If proximal thrombosis was found by ultrasound, inferior vena cava filter was placed before surgery. After surgery, weight loading should be avoided within 1 month, but active and passive flexion and stretch of ankle was allowable in bed. For patients with RAPT score of >5 after surgery, physical prophylaxis of DVT was employed, and 4100 U low molecular weight heparin was administered twice a day for patients with thrombosis after extubation. Venous blood was collected in the morning 2 days after admission and detections were conducted within 1 h. Coagulation function detection was performed with CA1500 automatic coagulation analyzer (Sysmex, Japan). DD was measured by immunonephelometry. DD of 1.4 mg/L was regarded as positive.

Statistical analysis

IBM SPSS version 19.0 was employed for statistical analysis. Quantitative data were expressed as mean ± standard deviation (X ± SD) and tested for normal distribution. These data with normal distribution were compared with t test. Qualitative data were compared with chi square test or Fisher exact test. Different DD cut-off values were used, the corresponding sensitivity (true positive rate) served as the longitudinal coordinate and 1-specificity (false positive rate) as the horizontal ordinate for the delineation of receiver operating characteristic (ROC) curve. Area under ROC curve, corresponding standard error, *P* value and 95% confidence interval (CI) were calculated. A value of $P<0.05$ was considered statistically significant.

Results

Incidence of DVT

In these patients, a total of 21 patients were diagnosed with DVT (24.70%). Of them, DVT was found in 15 patients before surgery (17.64%) (distal end: n=13; proximal end: n=2; post-operative absence of DVT: n=7) and 14 patients after surgery (16.47%) (new DVT: n=6; distal end). All DVT patients received therapy. In 2 patients with proximal thrombosis, inferior vena cava filter placement and subcutaneous injection of low-molecular weight heparins at therapeutic dose were performed before surgery, and thrombosis was absent after surgery. None died in this study and adverse events such as bleeding were not observed in these

Table 2. Age and incidence of DVT in different groups

Characteristics	Thrombosis	Non-thrombosis	P	F/X^2
Mean age	54.14±11.60	40.73±14.86	0.000	3.771
RAPT score (before surgery)				
Low risk	0	18	-	
Middle to high risk	15/67 (22.39%)	52	0.033	
RAPT score (after surgery)				
Low risk	0	13	-	
Middle to high risk	14/72 (19.44%)	58	0.114	

Table 3. Plasma DD at different time points after admission (mean ± SD, mg/L, n=85)

Group	2 days after admission	1 day before surgery	1 day after surgery	3 days after surgery	5 days after surgery
Thrombosis	5.81±5.38	4.98±4.74	5.69±4.60	5.40±6.95	5.08±2.68
Non-thrombosis	6.04±8.03	3.05±2.38	4.20±4.84	4.12±3.09	3.92±4.13
t	1.402	13.417	1.038	4.014	0.099
P	0.903	0.016*	0.220	0.244	0.232

Note: P<0.05 between thrombosis group and non-thrombosis group.

Table 4. Plasma DD and DVT diagnosed by ultrasound examination of lower limb veins

Plasma DD	Ultrasound examination		Total
	Positive	Negative	
Positive	14	66	80
Negative	2	5	5
Total	16	69	85

patients. The incidence of DVT according to the etiology of fracture and type of ankle fracture is shown in **Table 1**. The age and incidence of DVT in different groups are shown in **Table 2**.

Plasma DD before and after surgery

The plasma DD showed normal distribution. The increase of plasma DD was found in 65 patients (5.98±7.42 mg/L, 76.47%) 2 days after admission, 62 patients 1 day before surgery (3.53±3.21 mg/L, 72.94%), 71 patients 1 day after surgery (4.57±4.80 mg/L, 83.53%), 77 patients 3 days after surgery (4.43±4.36 mg/L, 90.59%) and 80 patients 5 days after surgery (4.21±3.84 mg/L, 94.12%). Of 3 patients with DVT before surgery (1 at admission), none developed increased DD; of 2 patients with DVT 1 day after surgery, none had increased DD. Patients were divided into thrombosis group and non-thrombosis group, the plasma DD in thrombosis group was significantly higher than that in non-thrombosis group 1 day before surgery, but no significant difference was observed at other time points between them (**Table 3**). The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of plasma DD were 87.5%, 4.3%, 20%, 17.5% and 83% in the diagnosis of DVT of ankle fracture patients (**Table 4**). The AUC was 0.645, suggesting that plasma DD has clinical importance in the diagnosis of DVT of PAF patients although it has a low diagnostic accuracy (**Figure 1**). According to the ROC, AUC was the largest when the cut-off value of DD was 3.6 mg/L at which the sensitivity and specificity were 0.810 and 0.578, respectively.

Discussion

DVT in patients with PAF

When PAF occurs, patients usually require long term movement restriction, and severe local soft tissue edema further causes poor blood flow. In addition, fracture may directly or indirectly stimulate adjacent veins, causing damage to or rupture of these veins. The hypercoagulable status is present immediately after injury and persistent during the perioperative period [3, 4]. Thus, there is a pathological basis for the development of DVT in patients with PAF. To date, few studies have been conducted to investigate DVT in PAF patients, and most studies focused on DVT in patients with fracture distal to the knee [5, 6]. Results of this study showed incidence of DVT was 24.7% in PAF patients, which was slightly higher than previously reported (2-14%) [7-12], but lower than that in patients with other fractures (such as hip fracture and peri-knee fracture) [13-16]. This might be ascribed to that PAF is mainly caused by non-high energy injury which has less injury to surrounding soft tissues and

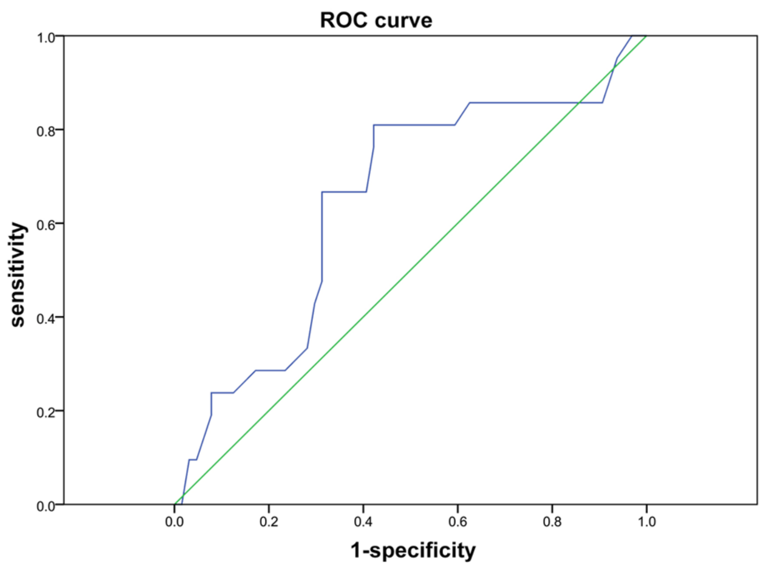

Figure 1. ROC curve of different DD cut-off values. The corresponding sensitivity (true positive rate) served as the longitudinal coordinate and 1-specificity (false positive rate) as the horizontal ordinate for the delineation of ROC. The AUC was 0.645.

blood vessels, and thus coagulation activation is limited due to small blood loss.

In the present study, 90.48% (19/21) of DVT patients had distal thrombosis, suggesting a low harm, and patients with distal thrombosis did not develop proximal thrombosis again. Macdonald et al investigated 135 patients with DVT [17] and found only 3% of patients with asymptomatic distal DVT developed proximal thrombosis. A majority of studies proposed that routine anti-coagulation for prevention of thrombosis was not necessary for patients with ankle fracture [6, 18]. If anti-coagulation is performed in all the patients with PAF, it may cause adverse events such as bleeding at the surgery site [19]. Of note, in the present study, inferior vena cava filter was placed before surgery in 2 patients with severe proximal thrombosis (external iliac vein, femoral vein and deep femoral vein), and ultrasound 3 days after surgery showed absence of proximal thrombosis, which might be ascribed to the embolus falling off. Thus, it was speculated that the prevention of DVT should not be neglected although it had a low incidence and the distal thrombosis was the dominant type of DVT. Measures should be taken to actively prevent progression into post thrombotic syndromeal though it has a low risk for PE, which has no influence on the patients' recovery and functional excise.

In all the patients with thrombosis, type of ankle fracture was not related to DVT, but patients with ankle fracture due to high energy injury were more likely to develop thrombosis as compared with patients with non-high energy injury. Kock et al [20] proposed that high energy injury increased risk for DVT.

Prognostic value of RAPT in DVT

It can be recommend that RAPT scoring is performed in patients with PAF according to expert consensus on the screening and therapy of deep vein thrombosis in patients with fracture [21]. Patients may be divided into low risk group (RAPT score of <5). Patients with middle to high risk for DVT should be closely monitored and prevention of DVT may be employed if necessary. As shown in **Table 1**, results showed that incidence of DVT was different between middle to high risk group and low risk group ($P<0.05$), and 2 patients with proximal thrombosis were included in middle to high risk group. Thus, it can be postulated that RAPT score is closely related to DVT before surgery, and may be used for effective prediction of DVT after admission in PAF patients.

However, the incidence of DVT was comparable between low risk group and middle to high risk group after surgery ($P>0.05$), which might be explained that RAPT score generally summarized the iatrogenic injuries, and some other risk factors such as tourniquet, methods of anesthesia and massive blood transfusion [22-24] were also related to DVT, but not included in RAPT scoring system.

Diagnostic value of DD in DVT of PAF patients

DD is a specific product of cross-linked fibrin after degradation by plasmin and the plasma DD increased significantly in patients with acute thrombosis [25, 26]. In addition, plasma DD also elevated dramatically after trauma, surgery, malignancy, inflammation, infection and DIC and in subjects with pregnancy or advanced age. Thus, the specificity of DD is low in the diagnosis of DVT. Clinically, plasma DD is used as an exclusion criterion in the diagnosis of thrombosis in patients after severe trauma or major surgery [27]. However, for patients with fracture due to non-high energy injury, the accuracy and specificity of DD are required to be confirmed in the diagnosis of DVT.

As shown in **Table 3**, significant difference in plasma DD was found only 1 day before surgery between two groups and the plasma DD in thrombosis group was significantly higher than that in non-thrombosis group. As shown in **Table 4** and ROC curve, the plasma DD at the calculated cut-off value has a sensitivity of 87.5 and specificity of 4.3, which were lower than those in patients with other fractures of lower limbs [1]. Moreover, the AUC was only 0.645. Thus, we speculated that plasma DD has a limited value in the diagnosis of DVT in PAF patients. Rafee et al [28] found the plasma DD was comparable between DVT patients and non-DVT patients after total hip arthroplasty and total knee arthroplasty.

It has been shown that the specificity of DD was poor, but its sensitivity was relatively high [29]. Bradley et al [30] investigated 138 patients with suspected DVT (non-traumatic fracture), and their results showed the sensitivity and specificity of plasma DD were 97.7% and 48.9% in the diagnosis of DVT. In this study, the sensitivity of plasma DD was also low in the diagnosis of DVT of PAF patients. Jennersjo et al [31] proposed that the size and location of thrombus could affect the sensitivity of plasma DD in the diagnosis of DVT, and its sensitivity for proximal DVT was significantly higher than for distal DVT. In the present study, most patients were diagnosed with distal DVT. In addition, there is evidence showing that the use of anti-coagulation therapy may also reduce the sensitivity of plasma DD in the diagnosis of thrombosis [32, 33]. In this study, all the patients with thrombosis received anti-coagulation therapy, which may be one of reasons for low sensitivity.

In our hospital, the plasma DD higher than 1.4 mg/L is regarded positive, but its specificity is only 4.3%. It is postulated that this may be attributed to the unreasonable cut-off value of plasma DD. Thus, ROC analysis was performed, and results showed the diagnostic value was the highest when the cut-off value of plasma DD was 3.6 mg/L at which the sensitivity and specificity were 0.81 and 0.578, respectively, similar to previously reported [29, 34].

Limitations

This was a retrospective study and a single center study, and the sample size was small, which may bias the results. More prospective studies with large sample size are required to confirm these findings. In addition, ultrasound inspection of the lower limb was employed as a diagnostic criterion for DVT because it is non-invasive, economic, and safe, but it has a low accuracy as compared to angiography as a gold standard. This may also bias the findings.

Conclusions

Patients with PAF have a risk for DVT in perioperative period, with distal embolization as the major type, and several PAF patients have a high risk for DVT. The incidence of DVT is comparable among patients with PAF of different types, but DVT is related to the energy of attack causing PAF. RAPT is associated with DVT before surgery, but not after surgery, in PAF patients. D-dimer has a low accuracy and a poor specificity in the diagnosis of DVT of PAF patients, and 3.6 mg/L is the optimal cut-off value of D-dimer in the diagnosis of DVT.

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Disclosure of conflict of interest

None.

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