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Research progress of D-dimer in the diagnosis of perioperative lower limb deep vein thrombosis in fracture

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Abstract: *Deep vein thrombosis is a disorder of venous return caused by abnormal intravascular coagulation, which has a high perioperative incidence in orthopedic patients and can develop into venous thrombosis syndrome and even fatal pulmonary embolism in severe cases. As a specific marker of thrombosis, D-dimer is widely used in diagnosing perioperative deep vein thrombosis in fractures, but its specificity in clinical diagnosis is low. It is often necessary to combine dynamic monitoring, ultrasound, Wells score, fibrinogen, and homocysteine to improve the accuracy of diagnosis. The authors have searched the literature and compiled a review of the latest research on D-dimer in diagnosing and managing deep vein thrombosis for clinical reference.*

Keywords: *D-dimer; perioperative fracture; deep vein thrombosis; diagnosis*

1. Introduction

Deep venous thrombosis (DVT) is a venous return disorder caused by abnormal blood clotting in the deep venous vessels, often in the lower limbs [1]. DVT can develop into a post-thrombotic syndrome of the lower limbs, which can also lead to lower limb dysfunction and even disability, and may lead to fatal pulmonary thromboembolism (PTE) if it is not diagnosed and treated effectively in the acute phase [2]. The leading causes of venous thrombosis are slow venous blood flow, damage to the venous vessel wall, and hypercoagulability of the blood. Fracture patients are subject to trauma, stress, prolonged bed rest, and braking, making the incidence of perioperative lower limb DVT high.

The typical clinical manifestations of lower limb DVT are swelling, fever, redness, edema, pain, and pressure in the affected limb, but most patients do not show specific symptoms in the early stages of the disease. The clinical manifestations and signs are not obvious, and the percentage of patients with DVT who have typical symptoms such as pain and swelling in the lower limb is not high. This makes it difficult to diagnose the condition promptly, affecting the diagnosis and management.

The fibrinolytic system produces D-dimers through the breakdown of ordered biochemical reactions. The higher the D-dimer value, the more likely a patient has venous thrombosis and the higher the sensitivity of its use in diagnosing acute deep vein thrombosis [3]. Independent use of D-dimer is highly accurate in the diagnosis of DVT and may reduce the need for unnecessary imaging to a certain extent. In current clinical practice, monitoring D-dimer levels is often used to predict and diagnose the occurrence of DVT in orthopedic patients. This allows for early diagnosis and individualized treatment.

It is generally accepted that serum D-dimer concentrations ≥0.5 mg/L are associated with a significantly higher likelihood of DVT and that this dichotomous approach can screen for an increased incidence of DVT [4].

However, in addition to deep vein thrombosis, increasing age and different fracture sites are also physiological and pathological factors that alter the concentration of D-dimers.

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2. Factors that affect D-dimer levels

2.1 Effect of age on D-dimer levels

Age has some influence on both D-dimer concentrations and the incidence of deep vein thrombosis. There is a significant difference in D-dimer levels in people over 70 years of age compared to those under 50 years of age, and even in healthy people, D-dimer levels are half as likely to be higher than the threshold in high-risk groups when they are over 70 years of age [5]. Age-adjusted cut-off values are now commonly used to reduce the effect of age on the diagnosis of deep vein thrombosis by D-dimer. Age-adjusted for patients >50 years of age with suspected DVT can be diagnosed as unfavorable if the D-dimer concentration is < (age × 0.01 mg/L) [6]. In a study of 697 outpatients with suspected DVT, Han Chengwu et al.[7] found that the specificity of the diagnosis was 84.1% after age-adjusted values, which was 6.6% higher than before age adjustment, but the sensitivity did not change significantly. Thus, although the age-adjusted strategy can somewhat circumvent some of the problems of age in diagnosing DVT using monitoring of D-dimer levels, its usefulness and reliability in clinical practice still need to be improved.

2.2 The effect of different fracture sites on D-dimer levels

Some studies have found that the incidence of DVT varies to a greater or lesser extent between fracture sites. In a study by Wang Hu et al. [8] of 1825 patients with lower limb fractures, the incidence of hip, femoral stem, tibial plateau, tibial stem, patella, and peri-ankle was 6.5%, 14.5%, 4.5%, 4.6%, 1.7%, and 2.0%, respectively, in 792 patients diagnosed. A study by Zhang Wenjuan et al.[9] on 462 fracture patients also confirmed a more significant difference in the incidence of deep vein thrombosis in patients with different fracture sites. The degree of fracture varies by fracture site, thus showing a tendency for the D-dimer level to increase significantly with the degree of fracture. Li Yan et al.[10] found that perioperative plasma d-dimer monitoring in 160 patients with fractures showed pelvic fracture patients > spine patients > lower limb fracture patients.

The specificity of d-dimer for diagnosing deep vein thrombosis was significantly lower. There was a false positive rate because of the multiple factors that influence the elevation of d-dimer. This suggests that although D-dimer is a sensitive marker of DVT formation, the specificity of D-dimer in the diagnosis of DVT is low, and the use of D-dimer monitoring alone cannot confirm the formation of DVT in the lower limbs, which to some extent affects its clinical diagnostic need.

To improve the objectivity and accuracy of D-dimer for diagnosing DVT, dynamic monitoring, D-dimer combined with Wells score, ultrasound, fibrinogen, and homocysteine are often used.

3. Retection Method

3.1 Dynamic monitoring of D-dimer

Orthopedic perioperative and surgical procedures can cause varying degrees of trauma to patients, resulting in abnormalities in coagulation, which can lead to a sharp increase in D-dimer concentrations, significantly above normal levels. The use of dynamic monitoring of D-dimer concentrations is helpful for the timely and definitive diagnosis of deep vein thrombosis. The current time frame for active tracking of D-dimer concentrations is generally the first, third, seventh, and fourteenth postoperative days, with a general fluctuating increase in D-dimer concentrations. The sensitivity of D-dimer concentration in the postoperative period is more sensitive on the third and seventh day; therefore, we should pay more attention to the D-dimer concentration on the third and seventh day in clinical practice [11]. Japanese scholars have proposed screening criteria for post-traumatic venous thromboembolism: (1) length of stay ≥5 days, (2) increased D-dimer concentration within three measurement days, and (3) D-dimer level ≥15 μg/mL [12]. It is informative for the clinical diagnosis of deep vein thrombosis.

3.2 D-dimer combined with Wells' score

The Wells scale is used to predict the risk of DVT in patients with suspected DVT and is easy to perform, relatively intuitive and concise, and requires less expertise from the clinician. For outpatients or patients uncomfortable with further testing, the Wells rule can stratify patients and allow for delayed testing in low and intermediate-risk patients, who can be safely and rapidly discharged from the

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hospital. Deep vein thrombosis can be more safely excluded using D-dimer levels in combination with the Wells criteria probability score. Niu Hui et al.[13] had a sensitivity of 93.75% in diagnosing the occurrence of DVT by combining D-dimer monitoring with the Wells score in 210 orthopedic patients at 7 days postoperatively. A study by Tanapong et al.[14] of patients with negative Wells scores but positive D-dimer levels (D-dimer ≥ 500 mg/L) found a DVT incidence of 5.18%. However, after adjusting the positive D-dimer as of value to 1.251 mg/L, the sensitivity and specificity for the diagnosis of DVT were 100% and 66.67%, respectively. Due to the limited sample size of this study (86 cases), its reliability remains to be further investigated. It can be seen that D-dimer monitoring combined with Wells' score can be more effective in excluding people at low risk of DVT, thus improving the efficiency of clinical management. However, the Wells score also has the disadvantages of being subjective and less effective in predicting or diagnosing DVT, which makes the reliability of diagnosis based on clinical symptoms and signs insufficient.

3.3 D-dimer combined with ultrasound

In patients with a low probability of deep vein thrombosis but a positive D-dimer, imaging techniques are required to clarify the diagnosis further. Venography is currently recognized as the 'gold standard' for the diagnosis of venous thrombosis. Still, it is an invasive test that can cause damage to the vessel wall and has problems with nephrotoxicity and allergy to the contrast medium [15]. There are limitations to its use.

Venous thrombosis in the lower limbs can lead to an increase in deep venous pressure and obstruction of blood flow, causing excess tissue fluid and tissue edema. Ultrasound is efficient, non-invasive, relatively inexpensive, easy to perform, and can be repeated. It also provides a clear and accurate picture of the specific condition of the veins in the lower limbs, which is ideal for diagnosis [16] and can be used alone to rule out venous thrombosis. However, there is a certain degree of underdiagnosis in patients with asymptomatic DVT.

In a study of 70 patients with spinal injuries, ultrasound combined with D-dimer monitoring was found to increase the detection rate of DVT by 4.1% compared to D-dimer monitoring alone [17]. In a study of 1821 patients with a high probability of lower extremity DVT who underwent D-dimer monitoring and lower extremity DVT ultrasound, Hang Xin et al.[18] showed that the combination of D-dimer monitoring and lower extremity DVT had a positive value and sensitivity of 100%, a negative predictive value of 99.1% and a sensitivity of 98.0%. This shows that D-dimer combined with ultrasound has a reliable detection effect in diagnosing deep vein thrombosis.

3.4 D-dimer combined with fibrin

Plasma fibrinogen (FIB) is an acute time-phase protein secreted by the liver in situations such as stress and infection. When the coagulation system is activated, thrombin production increases, and, with it, fibrinolysis leads to a rise in FIB levels, and therefore FIB can predict whether the blood is hypercoagulable [19]. Fibrin monomer monitoring is currently used to overcome the false positive D-dimer phenomenon seen in some patients.

In a study of 97 postoperative orthopedic patients by Liu Liqing et al. [20], serum fibrin levels were significantly higher on postoperative days 1 and 3 in 22 patients who developed thrombosis compared to 75 patients who did not develop thrombosis. In a study by Yang Dongwen et al.[21] comparing fibrin and D-dimer levels in 60 elderly patients with lower limb fracture surgery and 60 healthy patients at the same time, it was found that fibrin and D-dimer levels were significantly higher in patients with deep vein thrombosis than in the healthy population. It is evident that fibrin and D-dimer testing is a good indicator of fibrinolysis and coagulation in the body and aids in diagnosing DVT formation.

3.5 D-dimer combined with homocysteine

Homocysteine (Hcy), a sulfur-containing amino acid produced while converting the essential amino acid methionine to cysteine, has been well-documented as a risk factor for cardiovascular disease and can be used as a marker to predict DVT in patients undergoing lower limb fracture surgery [22]. There has been good progress in recent years in the use of Hcy for the diagnosis of DVT. Shu Junfeng et al.[23] compared homocysteine and D-dimer levels in 80 patients with thrombosis in orthopedics and healthy patients at the same time and found that homocysteine and D-dimer levels were higher in patients with deep vein thrombosis than in the healthy population, and the AUC, sensitivity, and specificity of the

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combined test were 94.7%, 92.5% and 88.7%, respectively, for the diagnosis of lower deep limb vein thrombosis. Zhang Lei suggested no significant correlation exists between homocysteine values and thrombus width, diameter, and size [24].

4. Discussion

In clinical practice, monitoring serum D-dimer levels combined with the Wells score can provide initial screening and improve diagnostic efficiency in patients with a low likelihood of lower limb deep vein thrombosis. If necessary, ultrasound or further venography can confirm the diagnosis and guide the prevention of possible venous thrombosis and the treatment of existing thrombosis. D-dimer monitoring is currently the most common predictive and diagnostic method in clinical practice, with good sensitivity and limitations, which are usually addressed by dynamic monitoring of D-dimer, with age-adjusted thresholds, combined with ultrasound if necessary. It is also essential to be alert to the differences in D-dimer levels arising from different fracture sites. In more complex conditions, a combination of diagnostic methods is often required to clarify the diagnosis further. In recent years, prospective studies have shown that D-dimer monitoring in combination with other serum proteins has significantly improved the accuracy of predicting and diagnosing deep vein thrombosis.

It is expected that this paper will be helpful for future clinical work.

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