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Efficacy of Drug Prophylaxis of Deep Venous Thrombosis during Perioperative Period of Total Knee Arthroplasty

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Abstract: To study the application of anticoagulant drugs in patients with kneeosteoarthritis (KOA) during perioperative period, and prevent the occurrence of deep venous thrombosisDVT in patients after Total knee arthroplastyTKA. In recent years, TKA has gradually become a routine orthopedic surgery. Due to the increase of surgery in clinical patients, postoperative clinical complications have become a problem that we should pay attention to. Especially lower extremity VTE and DVT are important problems for hospitalized patients. It is hoped that through scientific and technological progress and accumulation of clinical experience, the clinical incidence of DVT in patients after KOA can be further reduced, so that patients can successfully pass the recovery period. This article reviews the application of anticoagulants to prevent DVT after knee arthroplasty, aiming to provide reference for clinicians.

1. Introduction

With the aging of the population, KOA has become a common joint inflammation, causing pain and swelling of the knee joint, which is an important cause of mobility disorders and reduces the quality of life of patients [1]. For patients with KOA, reasonable treatment should be taken as soon as possible, and surgery should be taken if the effect of conservative treatment is poor. TKA [2] is a common treatment for end-stage KOA. TKA has been widely used in developed countries [3], which has a significant effect on improving OA and the quality of life of patients. However, with the increasing number of TKA surgeries in clinical practice, the main reason affecting the surgical effect is postoperative complications [4]. As a common complication after TKA, DVT [5] has attracted more and more attention. At present, there is still no unified gold standard for the treatment of VTE and DVT after TKA. Clinically, effective treatments are still being explored.

At present, drug anticoagulation [6] has become an important treatment for preventing VET and DVT. Unfractionated heparin (UFH) was treated with continuous intravenous infusion, and low molecular weight heparin (LMWH) [7] was administered by injection. Acetylsalicylic acid(aspirate), Apixaban [8], Rivaroxaban [9], and Dabigatran Etexilate [10] take orally. With continuous intravenous

therapy, the key is mandatory venous angiography of the lower extremity, which may be defined differently by different physicians in the clinic and rarely performed during the perioperative period. Therefore, the effect of new oral anticoagulant (NOAC) [11] on VTE and DVT is not certain, and direct comparison of the drugs cannot be made. This paper makes a literature review on the use of traditional anticoagulants and new anticoagulants to prevent VTE and DVT in patients undergoing KOA, and expounds the current clinical solutions to this problem.

2. Traditional anticoagulants

2.1. Unfractionated heparin, UFH

The function of UFH [12] is to bind and inactivate thrombin and enhance ATIII, thereby inhibiting the activities of coagulation factors IIa, IXA, Xa and plasmin, which is the cause of anticoagulation. However, as a traditional anticoagulant drug, UFC is easy to cause bleeding in patients. Ordinary heparin has an antidote [13], which can neutralize the anticoagulant effect of heparin. It plays a major role in thromboembolic diseases, cardiovascular and cerebrovascular diseases and hemodialysis. D2 polymers, activated partial thromboplastin time (APTT) and platelet count should be measured properly when used, and the dosage and time of drug should be adjusted reasonably. Long time application should also be careful of individual differences resulting in frequent bleeding and other adverse reactions. However, as an anticoagulant, UFH can reduce the incidence of pulmonary embolism (PE) [14], VTE and DVT, but studies have found that UFH cannot reduce the mortality of postoperative patients [15]. Thirty years ago, UFH was used to prevent VTE and DVT during the perioperative period of major orthopedic surgery [16], and its anticoagulant effect was relatively poor compared with LMWH. Therefore, LMWH is commonly used during the perioperative period of orthopedic surgery at present [17].

2.2. Low molecular weight heparin, LMWH

Compared with UFH, LMWH is widely used in clinical practice and is currently a first-line anticoagulant drug [18]. When administered by subcutaneous injection in clinical practice, LMWH can achieve significant effects by inhibiting the activities of Xa and IIA coagulation factor [19]. At the same time, without laboratory monitoring, LMWH has very good safety, high bioavailability and short half-life. It can significantly reduce the clinical incidence of VTE and DVT after TKA [20]. However, the administration method and use time of subcutaneous injection are long, and many patients refuse or interrupt treatment because of poor compliance due to pain. In addition to pain, the need for specialized medical personnel to perform the injection, and the inability to inject themselves after discharge are also another reason for poor patient compliance. Improper use of LMWH can lead to massive bleeding in patients [21], damage to the medicinal site, purple, red and swelling at the injection site, and even purple induration after long-term use. Therefore, the clinical application of LMWH should consider the patient's skin condition and injection technique.

2.3. Acetylsalicylic acid, aspirin

Aspirin, as an antiplatelet agglutinating drug [22], can inhibit the metabolism of arachidonic acid and reduce the production of thromboxane A2 by irreversible acetylation reaction with the active part of serine of cyclooxygenase [23], inhibit the production of platelets and produce anticoagulant effect. At present, it is believed that aspirin has great advantages in cardiovascular and cerebrovascular diseases, reduction of hemorrhagic complications [24] and anti-arterial thrombosis [25], and the multimodal anticoagulation regimen of aspirin after joint replacement has better

anticoagulation effect. At the same time, aspirin has analgesic effect, which is conducive to patients' early functional exercise [26], and can be taken for a long time with good tolerance and no need to monitor coagulation indicators [27], so it can be used as a routine anticoagulant after TKA. However, studies have found that the preventive effect of aspirin on DVT and PE is poor compared with LMWH, and aspirin is not recommended for patients treated with long-term anticoagulant drugs [28-29].

3. New anticoagulants

3.1. Apixaban

Apixaban, as a new type of anticoagulant directly administered by mouth, is a newly approved factor Xa inhibitor [30], which inhibits the active site of factor Xa [31] to prevent and treat VTE and DVT. ADVANCE 2 studies have shown that [32] Apixaban is used 12-14 hours after TKA, and 2.5mg is taken orally. The prevention effect of VTE and DVT is better than enoxparin, and the anticoagulant effect is reversible. It is less affected by other foods and drugs, and has high bioavailability. Patients with mild to moderate liver and kidney function impairment can also take it orally [33], which is partly metabolized by the kidney, and has good efficacy and safety compared with other anticoagulants [34], and the patient compliance is also good.

3.2. Rivaroxaban

Rivaroxaban, as the first direct oral factor Xa inhibitor [35], has been approved for anticoagulation after TKA in recent years, which has the advantages of rapid onset, good efficacy, high safety, convenient for patients to use, and no need to monitor prothrombin time (PT) and partial prothrombin time (PTT) during use [36]. The first dose of rivaroxaban 10mg was given 8h after operation, and lasted until 14 days after operation, once a day. Patients can take it before and after meals, which is less affected by diet [37] and can be cleared by kidney and liver. Studies have shown that rivaroxaban administration does not increase the incidence of bleeding events in patients after TKA [38]. Compared with enoxaparin administration, the risk of VTE is reduced by 52% [39], and the incidence of DVT, PE and all-cause death are reduced [40]. Jameson et al. [41] reported that rivaroxaban may increase the incidence of wound complications.

3.3. Dabigatran etexilate

Dabigatran [42] was first used to reduce the incidence of systemic VTE in the United States, and later used to prevent DVT and anticoagulation after TKA, and was approved by the Drug Administration (FDA) in 2010 [43]. The function is to block fibrinogen cleavage and bind to fibrin-specific sites of thrombin to play an anticoagulant effect. In 2015, the antagonist was approved by FDA and marketed, increasing the application prospect [44], and the safety of administration is also greatly increased. The advantages are rapid onset of effect [45], good curative effect, not affected by diet, and no need to monitor coagulation indicators during use. Studies have shown that [46] dabigatran acetate and enoxaparin have no difference in the prevention of DVT and PE after TKA, but have better effect in reducing the occurrence of VTE after TKA. The renal clearance rate of dabigatran axetil is about 80%. Patients with renal insufficiency need to be cautious when using dabigatran axetil. At present, there is no anticoagulant to reverse the anticoagulant effect [47], and the rate of indigestion is high after taking dabigatran axetil.

4. Clinical comparison of traditional and new anticoagulant drugs

Compared with new anticoagulants such as apixaban, rivaroxaban and dabigatran, traditional anticoagulants such as UFH, LMWH and aspirin [48], studies have found that [49] the anticoagulant effect of new anticoagulants is better. Patients after TKA were divided into two groups, and the anticoagulation effect of the two groups was compared [50]. In the ADVANCE 1 experiment [51], patients who received apixaban 2.5mg and enoxaparin 30mg twice a day after TKA were divided into two groups, and the anticoagulation effect was compared, and the results were not statistically significant. When enoxaparin 40mg is injected daily, oral apixaban [52] has better anticoagulant effect than enoxaparin injection. When LMWH and apixaban are used to prevent DVT in patients after TKA, the oral effect of apixaban is better and the use safety is higher.

Rivaroxaban [53] and heparin drugs can reduce the incidence of thrombosis and lower hospitalization costs in clinical application. Compared with rivaroxaban, the onset time of rivaroxaban is shorter, the effective standard of blood drug concentration can be reached in 2.5 hours, the oral bioavailability is close to LMWH, and the half-life is between 5.5 and 9 hours. Clinical studies [54] have shown that for patients after TKA with oral rivaroxaban, 1 tablet a day can well prevent the formation of DVT. Compared with LMWH that needs to be injected by medical professionals, patients are more likely to accept rivaroxaban by oral administration, which is excreted through urine and feces after taking it, with high clinical value and low nephrotoxicity. And the application is not subject to the age of patients and other factors. Studies have shown [55] that oral rivaroxaban is better than LMWH and aspirin in the prevention of DVT in patients after orthopedic surgery, and complications such as bleeding and wound do not occur.

However, some studies have shown [56] that the efficacy of new anticoagulants increases, and the risk of bleeding also increases. Study [57] the use of new anticoagulants in patients after TKA, and compare the preventive effects of new anticoagulants and traditional anticoagulants on VTE and DVT and the occurrence of complications. It shows that new anticoagulants have better effects, but bring a higher incidence of bleeding. Experiments [58] have proved that aspirin has higher safety; Rivaroxaban had better efficacy, but patients in the rivaroxaban group had increased rates of hidden blood loss and wound complications. It can be seen that the use of new anticoagulants still needs a lot of research and observation, and the existing controversy reminds clinical medical staff to be prepared and handle the risks when using them.

5. Summary and outlook

Clinically, there are more and more KOA patients, and the number of patients who choose TKA surgery is also increasing year by year. To prevent the occurrence of DVT, reduce the perioperative risk of patients, and use some anticoagulant drugs in a reasonable way have become the issues that clinicians need to pay attention to. New anticoagulants bring risks while improving efficacy, so LMWH is still the preferred anticoagulant [59]. However, after discharge, oral new anticoagulants are more convenient, which can reduce the trouble of continuous medication, increase the compliance of patients, and also facilitate the prevention of DVT after discharge. Therefore, when choosing drugs, clinicians should consider the efficacy, risk, patient's physical quality, economic conditions and other conditions to make the optimal choice.

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