Multimodal prophylaxis for venous thromboembolic disease after total hip and knee arthroplasty: current perspectives

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【Abstract】Life-threatening in the short term and leading to a high level of morbidity in the long term, venous thromboembolism (VTE) is the most fearful complication following lower limb arthroplasty. With advances in surgical procedure, anesthetic management and postoperative convalescence have altered the risks of venous thromboembolism after total joint arthroplasty in the lower extremity. The pathogenesis of VTE is multifactorial and includes the well-known Virchow’s triad of hypercoagulability, venous stasis and endothelial damage. Therefore, it is appropriate to use a multimodal approach to thromboprophylaxis. Despite extensive research, the ideal multimodal prophylaxis against venous thrombolism has not been identified. So this article reviews the recent developments in multimodal prophylaxis for thromboembolism after total joint arthroplasty.

Key words: Venous thromboembolism; Arthroplasty, replacement, hip; Arthroplasty, replacement, knee

Venous thromboembolic disease (VTED) is a serious and frequent complication of orthopedic surgery. Total joint arthroplasty in the lower extremity is an operation with a strong propensity for thromboembolic complications with potentially life-threatening consequences. Elective total hip arthroplasty (THA) and total knee arthroplasty (TKA) carry a high risk of postoperative venous thromboembolism (VTE), a serious and potentially fatal condition when it presents as deep vein thrombosis (DVT) and pulmonary embolism (PE). American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons have concluded that multimodal prophylaxis is the recommended safe and effective protection against thrombotic events.

Pathogenesis

The formation of thrombi is associated with Virchow’s triad of venous stasis, endothelial injury and hypercoagulability.

Stasis of blood may occur because of immobility, age, obesity, or disease processes. Venous stasis is particularly a problem in orthopedic surgery because of tourniquet use in TKA and positioning of the extremity in THA. The problem is compounded by stasis in the lower extremity caused by obstruction of femoral venous flow, either while the lower extremity is kept in an extreme position to provide adequate exposure for femoral preparation and hip component insertion or with the leg folded upon itself to gain exposure of the proximal tibia during knee replacement. It has been shown in vitro that obstruction of venous flow for just 10 minutes is enough to stimulate thrombus formation in the presence of a thrombogenic stimuli.

Damage to the epithelial cell lining of blood vessel is one of the extrinsic factors triggering the clotting cascade. The damaged endothelium attempts to maintain vascular integrity by adhesion and aggregation of platelets. As the clotting cascade continues, the final

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The step is the formation of thrombin, which leads to the conversion of fibrinogen to fibrin and the formation of a fibrin clot. Kinking of the femoral or popliteal veins during total hip and knee arthroplasty can produce endothelial injury, providing the nidus for the formation and propagation of clots.

Hypercoagulability may be caused by various disease processes and medications. It has been proved during the reaming of the femur and insertion of the implant in THA that there are increased numbers of prothrombin-F1.2, thrombin-antithrombin complexes and fibrin peptide A, which leads to hyper-coagulability. A relative hypercoagulable state can develop during the procedure because blood loss can result in reduction in antithrombin III and inhibition of the endogenous fibrinolytic system, which further promote thrombus propagation during the total hip and knee arthroplasty.

**Epidemiology**

In the 1970s, the incidence of symptomatic PE after THAs was reported to be as much as 8% in the absence of prophylaxis, with a fatality rate of 1%. The American National Institutes of Health Consensus Conference in 1986 further raised the general awareness of the high risk of DVT and PE and stratified patient risks by types of surgery. Based on data available at that time, orthopaedic surgery of the lower extremity, including TKA, THA, and hip fracture, were determined to present the highest risk for VTED without prophylaxis.

A number of risk factors for the development of DVT have been identified, including recognized clinical risk factors, controversial or weak risk factors, and genetic risk factors. However, even without underlying risk factors, patients who undergo total joint arthroplasty are at high risk for the development of VTE. More recent studies have reported that without the use of prophylaxis following THA, the prevalence of venographic VTE might be as high as 93% and fatal PE may develop in up to 2% of patients. From these data, we could consider that the morbidity of VTE is very high among the patients without prophylaxis after total joint arthroplasty.

Since surgical practice and postoperative care have substantially changed in the last 40 years as a result of improved knowledge on pathophysiology, kinematics and material science, it is likely that the morbidity of VTE after total joint arthroplasty has decreased. In a meta-analysis of 130,000 patients who had THA, Murray et al found that the overall mortality was 0.30% (10 of 3,355) among patients who did not receive prophylaxis, 0.40% (40 of 10,105) among those who received heparin, 0.29% (11 of 3,763) among those who received warfarin, 0.15% (4 of 2,649) among those who received aspirin, and 0.50% (13 of 2,618) among those who received dextran, respectively. Recently the reported incidence of fatal PE has been much lower (0-0.2%). In the UK, the 30-day incidence of fatal PE following TKA and THA was 0.07%; the overall death rate was 0.31% (13 of 4,253) and the rate of fatal PE was 0.07% (3 of 4,253). This is probably due to a combination of improved surgical technique of spinal anesthesia and early mobilization, rather than any prophylaxis for thromboembolism.

**Multimodal prophylaxis for VTE after total joint arthroplasty**

Nowadays, measures to prevent VTE after total joint replacement are almost universally used and probably the most widely disseminated guidelines are those proposed by ACCP. But some within the orthopaedic community have challenged these recommendations as being not entirely applicable to the patients undergoing THA and TKA. The two guides both suggest multimodal prophylaxis for thromboembolism after total joint arthroplasty, especially with high risk of bleeding.

**Anesthesia: regional anesthesia** Spinal anesthesia can reduce blood loss and transfusion requirement and increase lower extremity blood flow in comparison to general anesthesia. A number of studies have demonstrated a reduced rate of DVT after THA with spinal or epidural anesthesia. It has been postulated that the decreased rate of thrombosis in these patients may be secondary to improved blood flow in the lower extremities and a decrease in blood loss and transfusion requirements. Randomized trials have shown that regional anesthesia (spinal or epidural) reduces the risk of DVT (proximal and distal) and PE following hip surgery by 40%-50%.

The technique of hypotensive epidural anesthesia (HEA) increases lower extremity blood flow more than epidural anesthesia alone. Enhanced blood flow in the immediate postoperative period with HEA may be im-
portant as a bridging technique before pneumatic compression devices are instituted. In a study, the authors compared HEA and hypotensive total intravenous anesthesia (HTIVA) with propofol and remifentanil on blood loss during primary total hip replacement. The result showed that intraoperative blood loss, percentage of patients receiving blood substitution, and total packed red blood cells transfused were less in those patients receiving HEA than those receiving HTIVA ($P$=0.001, 0.04 and 0.015, respectively). Mean central venous pressure was lower in HEA group than in HTIVA group intraoperatively ($P$=0.019). Mean hemoglobin concentrations and coagulation were similar between two groups. Neurological examinations of all patients were intact in the postoperative period. In a continuous study, HEA can increase blood flow in lower extremity and reduce blood loss and transfusion requirement, so as to minimize venous stasis and venous thrombosis, which has proven to be safe in patients with hypertension, ischemic heart disease, chronic renal insufficiency, and in the elderly.

**Mechanical prophylaxis-intermittent pneumatic compression** The objective of mechanical prophylaxis is to substitute the action of the muscle pumps of the legs that are normally activated during ambulation. Intermittent pneumatic compression (IPC) involves applying cuffs to the limbs that are automatically inflated and deflated by a pump. Some researches have shown that the application of IPC immediately after operation increases the velocity and volume of venous flow, preventing or minimizing the formation and propagation of clots. Thus, the authors apply IPC as soon as the patient reaches the recovery room. Some authors have advocated IPC during surgery. More recently, some authors used portable pneumatic compression device to prevent VTED. In the study, the authors compared a miniaturized, portable, sequential, pneumatic compression device — ActiveCare continuous enhanced circulation therapy (CECT) system, Aqiva, Israel, with a non-mobile, nonsequential device on the ability to prevent postoperative DVT after joint arthroplasty. All patients were treated with low-molecular-weight heparin, application of any of the two devices perioperatively, and routine duplex screening. The result showed that the CECT system had better compliance (83% vs 49%), lower rates of DVT (1.3% vs 3.6%), reduction in clinically important PE (0 vs 0.66%), and shorter time length of hospital stay (4.2 days vs 5.0 days). The authors considered that the portable CECT system could be used with low-molecular-weight heparin for DVT prevention in high-risk orthopedic patients.

**Anticoagulants:** (1) **Aspirin** Aspirin prophylaxis is safe, well-tolerated, easy to administer and with prompt effect. It requires no monitoring, has analgesic and antipyretic effects and reduces the risk of ectopic ossification.

Pulmonary Embolism Prevention Trial conclusively established the beneficial role of aspirin in reducing the risk of postoperative thromboembolism. In this study, 160 mg of aspirin was administered preoperatively and continued for 35 days postoperatively in the patients undergoing hip-fracture surgery, hip arthroplasty and knee arthroplasty. Objectively proven and adjudicated symptomatic venous thromboembolic events up to the day of hospital discharge were collected. While the study demonstrated a statistically significant reduction in VTE in 13 356 patients with hip fracture, from 2.5% to 1.6%, no statistically significant reduction was observed in 2 648 patients undergoing hip or knee arthroplasty with 1.1% experiencing symptomatic VTE in the aspirin group compared with 1.4% in the placebo group. The Antiplatelet Trialists’ Collaboration assessed the efficacy of aspirin among other antiplatelet drugs in preventing DVT in 8 400 general surgical and orthopaedic patients included in 53 published studies. In this overall group, DVT was reduced from 34.8% to 26% ($P$<0.01), and PE was reduced from 2.7% to 1.0% ($P$<0.01).

In a study of 3 473 consecutive patients undergoing TKA, 95% were treated with a regional anesthesia, and all but 71 patients received aspirin (325 mg twice a day for 6 weeks) as VTED prophylaxis. Those patients not receiving aspirin were deemed to be at increased risk and received warfarin for venous thromboembolic prophylaxis. At only 6-week follow-up, fatal PE approximated 0.1% and readmission for nonfatal PE or proximal DVT occurred in 0.5% of patients; 8 patients (0.5%) required aspiration of the knee for a postoperative hematoma.

(2) **Low molecular weight heparin (LMWH)** The efficacy of LMWH is well documented. Eikelboom conducted a meta-analysis to examine post-discharge prophylaxis with LMWH after total hip replacement and...
demonstrated a reduction in symptomatic VTE from 4.3% to 1.4% with LMWH. Colwell and coworkers demonstrated a significantly lower rate of symptomatic VTE in THA patients with LMWH (enoxaparin 30 mg sc twice a day, 0.3%) than adjusted dose of warfarin (1.1%). There were more major bleeding in the LMWH group (1.2%) than in the warfarin group (0.5%), although this difference was not statistically significant (P=0.055).

In 2008, Sharrock et al reviewed publications over the last nine years and performed a meta-analysis of 28,038 patients which showed that PE occurs despite the use of anticoagulants, and LMWH is associated with the highest all-cause mortality of all the prophylactic agents. Neviaser et al examined the records of 135 patients who underwent total joint arthroplasty, experienced an in-hospital PE, and received treatment with enoxaparin at therapeutic doses (1 mg/kg body weight). The type and frequency of complications were determined and classified as major or minor. Twenty-seven percent of patients experienced minor complications and 10% experienced major complications. The incidence of major bleeding was substantially higher than rates reported for nonsurgical patients. The overall complication rate of enoxaparin treatment is similar to that reported for unfractionated heparin treatment in this setting, but the complications are less severe.

(3) Warfarin Over the past three decades, interrupted only by a transient surge in the popularity of fractionated heparins, warfarin has enjoyed increasing favor and is unarguably the most commonly used single agent in North America for prophylaxis of VTED following total joint arthroplasty.

In Lieberman et al’s study, between 1987 and 1993, 1,099 primary and revision THA were performed in 940 patients and the authors used low-dose warfarin for prophylaxis against thromboembolic disease. The average duration of prophylaxis was 15 days (range, 1-29 days). The result showed that 12 total hip arthroplasties were associated with a symptomatic PE; the overall prevalence of this complication therefore was 1.1% (95% confidence interval, 0.4% to 1.9%). Four pulmonary emboli were diagnosed before discharge and 8 after discharge. A fatal PE occurred (0.1%). Patients who had a history of symptomatic VTED had a significantly increased risk of symptomatic PE after THA (P=0.001). A major bleeding episode occurred after 32 total hip arthroplasties (2.9%). Patients who had a prothrombin time of more than 17 seconds had a significantly increased risk of hematoma formation (P=0.003). The author thought that prophylaxis with low-dose warfarin is safe and effective for the prevention of PE after THA.

In a series of studies, the authors used extended warfarin to prevent VTED in 3,293 patients undergoing total hip (n=1,972) or knee (n=1,321) arthroplasty from 1984 to 2003. The results showed that the overall readmission rate for VTE was 1.6% (38/2,449 patients who did not receive warfarin) and 0.2% (2/884 patients who received extended warfarin, P=0.0015) and readmission for PE 0 (0/844 patients who received warfarin) and 0.7% (17/2,449 patients who did not, P=0.01) after total hip and knee arthroplasties. So the authors thought extended low-intensity (international normalized ratio, 2.0) warfarin prophylaxis reduces readmission rates associated with all thromboembolic events (P=0.0015) and PE (P=0.01) after total hip and knee arthroplasty, with a low rate (0.1%) of clinically meaningful bleeding events.

Pendleton et al studied a single-center prospective cohort of consecutive (n=351) post–joint arthroplasty/revision patients who were initiated on warfarin using a new initiation nomogram and then discharged to home with home health services. The mean time to an international normalized ratio of 2.0 or higher was 5 days. The result showed that adverse events were uncommon: 4 patients (1.14%) had VTE, 1 (0.28%) had major bleeding episode, and 6 (1.7%) had minor bleeding. So the authors thought that specific warfarin dosing nomogram managed by an anticoagulation service and used in joint arthroplasty/revision patients who are discharged to home with home health services is effective anticoagulation with few associated adverse events.

(4) Direct factor Xa inhibitors Currently, there are two drugs within this class in clinical development.

The first drug, apixaban, is a small-molecule, oral, direct factor Xa inhibitor that selectively and reversibly inhibits both free factor Xa and prothrombinase activity. Apixaban has high oral bioavailability in large animals, and a half-life of approximately 12 hours in humans. It has been tested in subjects undergoing TKA in a large phase II randomized trial with promising results. The second drug is rivaroxaban, which is a small-
molecule, oral, direct factor Xa inhibitor that selectively and reversibly inhibits free and clot-associated factor Xa activity, as well as prothrombinase activity. Rivaroxaban has recently been approved for the prevention of VTE after total hip or knee replacement in European Union and several other countries, based on the results of the phase III record program, which comprised four large studies in more than 12,500 patients in total. The results of this study demonstrated that extended prophylaxis with rivaroxaban 10 mg/d was superior to short-term prophylaxis with enoxaparin 40 mg/d for the prevention of VTE, including symptomatic events, after THA. Despite rivaroxaban being given for 3 weeks longer than enoxaparin, the incidence of major bleeding at 5 weeks was 0.1% in both groups. This study confirmed the benefits of extended prophylaxis over short-term prophylaxis and the safety of its use.  

(5) Direct thrombin inhibitors (DTIs) DTIs are small molecules that inhibit thrombin directly, which allows them to inhibit both free and clot-bound thrombin. It constitutes a potential advantage over the indirect thrombin inhibitors.  

The first agent to be developed in this class was ximelagatan, a prodrug of the active form melagatan. Its mechanism of action involves a direct inhibition of the active site of thrombin in either its circulation or clot-bound forms, thus preventing the extension of a previously formed clot. Initial studies showed that this drug was efficacious and safe for VTE prophylaxis after orthopedic surgery; however, a meta-analysis showed that although in patients with THR the use of ximelagatan resulted in less VTE events compared with LMWH, it was associated with a 3.3-fold increase in major bleeding.  

Dabigatran etexilate is a prodrug of dabigatran, a specific and reversible thrombin inhibitor. Three phase III studies investigated oral dabigatran etexilate for the prevention of VTE after major orthopaedic surgery. These studies compared oral dabigatran etexilate 150-220 mg once daily with the subcutaneous LMWH. The result showed that dabigatran was either non-inferior or inferior to the LMWH enoxaparin with a similar safety profile.  

Multimodal thromboprophylaxis As mentioned above, the aetiology of VTE is multifactorial, including the well-known Virchow’s triad of hypercoagulability, venous stasis and endothelial damage. It is therefore appropriate to use a multimodal approach to thromboprophylaxis. The researcher continues for the ideal combination of agents and factors, including chemical, mechanical, surgical or anesthetic, which offers efficient thromboprophylaxis and is associated with the lowest incidence of adverse effects.  

Sarmiento et al investigated the effectiveness of aspirin, a program of intraoperative and postoperative exercises, and graded elastic stockings or intermittent compression devices as prophylaxis against thromboembolic disease in a series of 1,267 patients who had 1,492 total hip arthroplasties. Regional (epidural) anesthesia was used for 1,099 arthroplasties (73.7%), and general anesthesia was used for 393 procedures (26.3%). The result showed that a fatal PE occurred after two arthroplasties (0.13%), a nonfatal PE was diagnosed in 14 patients (0.94%), and DVT developed in 15 patients (1.01%). Compared with general anesthesia, the use of regional anesthesia was associated with a significantly lower rate of nonfatal PE (P<0.001) and DVT (P<0.025). So the authors thought the multimodal prophylaxis was effective and safe for venous thrombolism after THA.  

Dorr et al retrospectively reviewed the records on 1,179 consecutive total joint arthroplasties in 970 patients who underwent primary and revision total hip and knee replacement. Preoperatively, the patients were divided into two groups according to risk stratification. Eight hundred and fifty-six patients (1,046 operations) were considered to be at low risk and were managed with aspirin, dipyridamole or clopidogrel bisulfate as well as intermittent pneumatic calf compression devices. One hundred and fourteen patients (133 operations) were considered to be at high risk and were managed with low molecular weight heparin or warfarin and intermittent pneumatic calf compression devices. The results showed that there were 3 symptomatic pulmonary emboli (0.25%), and 5 clinically symptomatic deep venous thrombi (0.4%) and no fatal pulmonary emboli in both groups. Sixty-one asymptomatic deep venous thrombi (5.2%) were found with use of routine postoperative Doppler ultrasound scans.  

A series of clinical, basic and applied researches on thromboembolic disease after total joint arthroplasty were conducted in hospital for special surgery during
A multimodal prophylaxis protocol was developed for special surgery and fully implemented since 1995, consisting of stratifying the individual patient's risk and implementing a series of safe preventive measures before, during, and after surgery to reduce the risk of VTE and bleeding.

The measures include discontinuation of procoagulant medication and intraoperative intravenous heparin after acetabular work during THA, the use of pneumatic compression devices, elastic stockings, and frequent and vigorous dorsiflexion of the ankles and prompt mobilization of patients after surgery to diminish venous stasis. If these safe measures are observed, postoperative pharmacologic prophylaxis does not need to be aggressive in the patients without predisposing factors for VTE and since the mid 1970s, enteric-coated aspirin has been the authors' preferred postoperative chemoprophylaxis. The authors indicate warfarin for patients who have recognized predisposing factors for VTE or who were already prescribed warfarin for preexisting comorbidities.

Salvati et al have conducted retrospectively three decades of thromboprophylaxis research for total THA. According to the author's clinical experience, more than 5 000 total hip arthroplasties were performed during the last decade and closely followed up prospectively for a minimum of 3 months. The result clearly shows that with multimodal prophylaxis, the prevalence of thromboembolism is very low (the incidence of clinical DVT being 2.5%; symptomatic PE 0.6%). In a recent paper, also 10 000 total hip and knee replacements in Hospital for Special Surgery in New York, USA, demonstrates that the multimodal prophylaxis is safe and effective, resulting in a very low prevalence of thromboembolism, bleeding and all-cause mortality.

Conclusion
VTED continues to be a serious complication of total hip and knee arthroplasty. The pathogenesis of VTE is multifactorial and includes the well-known Virchow's triad of hypercoagulability, venous stasis and endothelial damage. Therefore, it is appropriate to use a multimodal approach to thromboprophylaxis.

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