Relationship Between Deep Vein Thrombosis and Pulmonary Embolism Following THA and TKA

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As a result of reading this article, physicians should be able to:

1. Recognize the clinical importance of an acute episode of venous thromboembolism and its potential long-term sequelae.
2. Know where venous thromboembolism is most likely to originate in orthopedic patients and the conditions in which it may become symptomatic.
3. Understand the clinical importance of pulmonary embolism and the conditions that may promote its development in patients undergoing orthopedic surgery.
4. Distinguish between the views of the AAOS and ACCP regarding the relationship between deep vein thrombosis and pulmonary embolism.

ABSTRACT

Patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are at risk for venous thromboembolisms, including deep vein thrombosis and pulmonary embolism. Most deep vein thromboses are asymptomatic, but they can lead to long-term morbidity to the same extent as symptomatic events. The risk of complications of venous thromboembolisms depends on the location of thrombi; potential long-term compli-

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Deep vein thrombosis and pulmonary embolism are major health concerns and are responsible for significant mortality, morbidity, and resource expenditure. Approximately 600,000 Americans suffer from venous thromboembolism each year, and at least 100,000 deaths are directly or indirectly related to this condition. Risk factors for venous thromboembolism include surgery, cancer, increasing age, obesity, and acute medical illness.

Major orthopedic surgeries, especially total hip arthroplasty (THA) and total knee arthroplasty (TKA), are particularly high-risk procedures for venous thromboembolism. In fact, deep vein thrombosis is one of the most common complications after THA or TKA. The incidence of clinically asymptomatic, objectively confirmed deep vein thrombosis in patients after THA and TKA was 40% to 60% in those not receiving thromboprophylaxis. Combined prevalence rates are reported to be 0.9% to 28% for pulmonary embolism and 0.1% to 2% for fatal pulmonary embolism following THA and TKA, respectively.

This article describes the natural history of deep vein thrombosis and pulmonary embolism in THA and TKA, examines deep vein thrombosis as a predictor of recurrent venous thromboembolism and pulmonary embolism, and describe the long-term sequelae of deep vein thrombosis and pulmonary embolism.

**Natural History of Deep Vein Thrombosis and Pulmonary Embolism**

In THA and TKA, Virchow’s triad—venous stasis, endothelial injury, and hypercoagulability—is involved in the formation of thrombi during the perioperative period. Blood flow disruption in the femoral vein leading to venous stasis may occur as a result of limb positioning during the procedure, localized postoperative swelling, and decreased postoperative ambulation. A significant reduction in venous capacitance and outflow occurs during THA and may be exacerbated during dislocation of the hip and insertion of the femoral prosthesis.

In addition, tourniquet use in TKA may increase the formation of lower-extremity thrombi. Endothelial injury may occur during positioning of the extremity with femoral vein kinking, thermal injury from bone cement, and calf vein distension. Hypercoagulability occurs as the result of local and systemic activation of coagulation intra- and postoperatively. Increased levels of multiple markers of thrombus generation, including prothrombin, thrombin–antithrombin, and fibrinopeptide A, have been demonstrated during the procedure.

These findings, along with venous ultrasound and venographic studies, provide strong evidence for a thrombogenic process that begins during the perioperative period. Using serial venography after unilateral TKA of 42 legs, Maynard et al found distal deep vein thrombosis in 45% and a popliteal thrombus in 5% of legs 24 hours postoperatively. However, although the thrombogenic process begins intraoperatively, venous thromboembolism risk extends anywhere from 3 to 6 weeks and thereafter postoperatively.

Studies of patient databases estimate that approximately 50% to 75% of surgery-related venous thromboembolism events occur after discharge. The median time until diagnosis of a symptomatic deep vein thrombosis has been found to be 21.5 days after THA and 9.7 days after TKA. Warwick et al found that the diagnosis of venous thromboembolism was made after hospital discharge in 2.3% (6639) of THAs and 1.7% (8326) of TKAs.

The risk of complications, including pulmonary embolism, depends on the location of the thrombi. Postoperatively, deep vein thrombosis usually begins in the veins of the calf, often originating in the valve cusps and 75% to 80% will occur in the operated leg. Calf thrombosis accounts for 50% to 80% of the overall frequency of thromboembolic disease after THA and TKA, respectively, whereas proximal deep vein thrombosis develops in 10% to 25%, respectively. Once the calf thrombus develops, it can further enlarge and propagate proximally. Studies using serial duplex ultrasound have observed propagation rates of 17% to 23% after THA and TKA, respectively. Although the majority of symptomatic episodes of deep vein thrombosis start in the calf veins, symptoms are uncommon until propagation to the proximal veins occurs.
Rates of symptomatic deep vein thrombosis after THA and TKA range from 2.1% to 12.5%, with 50% to 85% of events occurring proximal to the knee.\textsuperscript{19,20} If left untreated, approximately 50% of patients with symptomatic proximal deep vein thrombosis will develop a symptomatic pulmonary embolism\textsuperscript{13} and have a 5% to 10% risk of fatal pulmonary embolism.\textsuperscript{21}

**LONG-TERM SEQUELAE OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM**

Venous thromboembolism is a disease with long-term complications that include recurrent venous thromboembolism, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension.

**Recurrent Venous Thromboembolism**

Venous thromboembolism recurrences are common during the first 6 to 12 months after the first event, but the risk persists for several years.\textsuperscript{22-24} In a prospective cohort study, Prandoni et al\textsuperscript{25} followed 528 patients with first-episode deep vein thrombosis with at least 3 months of oral anticoagulant use and found a venous thromboembolism recurrence incidence of 24.3% after 5 years and 29.7% after 8 years. Twenty percent of the recurrent venous thromboembolism episodes were pulmonary embolisms, which were fatal more than half the time.\textsuperscript{25}

Several studies reported that patients who present with pulmonary embolism are at a greater risk for recurrent pulmonary embolism than are patients with an isolated deep vein thrombosis.\textsuperscript{26} These findings have led some to suggest that deep vein thrombosis and pulmonary embolism are distinct clinical entities with different natural histories.\textsuperscript{27} However, other studies suggest that patients with pulmonary embolisms and isolated deep vein thromboses may have a similar venous thromboembolism-specific prognosis. In a retrospective, population-based study of residents of an entire New England metropolitan area, Spencer et al\textsuperscript{27} found that isolated deep vein thromboses and pulmonary embolisms had similar incidence rates at 3 years postoperatively. The patients who presented with pulmonary embolisms or isolated deep vein thromboses experienced rates of subsequent pulmonary embolism and overall venous thromboembolism of 5.9% vs 5.1% and 15.0% vs 17.9%, respectively.\textsuperscript{27} Further study of the recurrence rates of patients who present with symptomatic pulmonary embolism vs isolated deep vein thrombosis is warranted.

It is critical to distinguish between idiopathic deep vein thrombosis or pulmonary embolism and deep vein thrombosis or pulmonary embolism with an identifiable medical cause, such as trauma or surgery.\textsuperscript{28-31} After an initial episode of deep vein thrombosis or pulmonary embolism, fatal pulmonary embolism is significantly less common if that event is caused by THA or TKA than if it is idiopathic.\textsuperscript{31} In comparing different types of operations, Hansson et al\textsuperscript{32} found a lower risk of venous thromboembolism recurrence among orthopedic surgery patients; the multivariate relative risk of recurrent venous thromboembolism was 0.21 (95% confidence interval [CI], 0.07-0.65; \(P = .07\)) after orthopedic surgery and 0.67 (95% CI, 0.27-1.64; \(P = .38\)) within 3 months after any other surgery. This evidence suggests the existence of unique coagulation factors associated with orthopedic surgery patients and procedures that should be further investigated.

**Postthrombotic Syndrome**

In addition to the risk of recurrent venous thromboembolism, patients with a venous thromboembolism may also develop postthrombotic syndrome, a chronic and potentially disabling condition characterized by edema, pain, venous ectasia, and, in severe cases, painful leg ulcers.\textsuperscript{33} With acute symptomatic deep vein thrombosis present, the incidence of postthrombotic syndrome symptoms have ranged from as low as 23% to approximately 65%.\textsuperscript{34} In a prospective study of 355 patients with symptomatic deep vein thrombosis, Prandoni et al\textsuperscript{25} observed a cumulative postthrombotic syndrome incidence of 17% after 1 year and 29% after 8 years of follow-up. Risk for developing postthrombotic syndrome after asymptomatic deep vein thrombosis is of particular interest in orthopedic surgery because the majority of deep vein thromboses that occur after TKA are asymptomatic. Siragusa et al\textsuperscript{35} evaluated 217 THA and TKA patients with asymptomatic deep vein thrombosis and found that 24% developed postthrombotic syndrome in the following 2 to 4 years. Similarly, in a series of 132 TKA and THA patients with asymptomatic deep vein thrombosis who were followed for 18 months, Schindler and Dalziel\textsuperscript{36} found a postthrombotic syndrome incidence rates of 16.7%.

However, Ginsberg et al\textsuperscript{37} suggested that the risk for symptomatic postthrombotic syndrome after THA and TKA in asymptomatic deep vein thrombosis patients tends to be lower. In their study, 255 patients who underwent THA or TKA within the previous 2 to 7 years had postthrombotic syndrome incidence rates between 4% and 6%.\textsuperscript{37} The authors proposed that these lower rates were due to the use of prophylaxis to reduce the incidence of venous thromboembolism and the subsequent risk of associated complications.\textsuperscript{37} Also, all patients in the study with asymptomatic deep vein thrombosis received warfarin for 6 to 12 weeks regardless of the location of thrombi, whereas only the proximal thrombi patients in the study by Schindler and Dalziel\textsuperscript{36} received warfarin; those with distal thrombi received aspirin after hospital discharge. Although most asymptomatic deep vein thromboses will not cause acute pulmonary embolism, these studies suggest its clinical importance.

**Chronic Thromboembolic Pulmonary Hypertension**

Chronic thromboembolic pulmonary hypertension may occur following a single...
or recurrent episode of pulmonary embolism, and if it is left untreated, progressive right ventricular dysfunction with ultimate right heart failure can occur. Estimates of the incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism range from 0.5% to 3.8%.

For every 100 cases of pulmonary embolism, 3 cases of chronic thromboembolic pulmonary hypertension will occur, with a cumulative incidence of 1% to 5% within 2 years after the embolic event. In addition, approximately 40% of chronic thromboembolic pulmonary hypertension cases originate from asymptomatic venous thromboembolism.

Deep Vein Thrombosis as a Predictor of Subsequent Venous Thromboembolism

Rates of asymptomatic deep vein thrombosis without prophylaxis in THA and TKA range from 20% to 58%, with 1.5% to 8% detected in the femoral vein. Even with the use of prophylaxis, rates of asymptomatic deep vein thrombosis remain high at 34% to 61%, of which 2.5% to 9.1% are located proximally to the knee. In a study exploring the relationship between asymptomatic deep vein thrombosis and symptomatic venous thromboembolism in patients undergoing THA and TKA who received prophylactic enoxaparin, Quinlan et al determined that the ratio of asymptomatic deep vein thrombosis at hospital discharge to symptomatic venous thromboembolism within the next 3 months was approximately 5:1 for THA and 21:1 for TKA.

It is well recognized that patients with symptomatic deep vein thromboses are at increased risk of developing symptomatic or fatal pulmonary embolism. However, in many cases, the deep vein thrombosis is silent, and the clinical presentation of pulmonary embolism remains variable. Clinical signs suggestive of pulmonary embolism are not specific but may include tachycardia, dyspnea, rales, chest pain, fever, and neck vein distention. Even when a precise clinical diagnosis of thromboembolism is lacking, vague symptoms such as unilateral leg swelling or unexplained tachycardia warrant a thorough physician workup.

Kim et al conducted a randomized, controlled, prospective trial that showed that no elevated risk of symptomatic or asymptomatic pulmonary embolism was associated with calf thrombi in post-THA patients who did not receive deep vein thrombosis prophylaxis. Of the 300 THA (200 bilateral and 100 unilateral) patients in the study, venographic studies at 6 or 7 days postoperatively showed the presence of calf thrombi in 22 (11%) and 8 (8%) bilateral and unilateral patients, respectively. Lung perfusion scans were negative in these thrombotic patients on their seventh or eighth postoperative day, and on repeat postoperative scanning of these same patients at 6 months.

According to the American Academy of Orthopaedic Surgeons (AAOS), a lack of consistent evidence exists establishing the association between symptomatic deep vein thrombosis and pulmonary embolism in patients undergoing THA and TKA. Parvizi et al conducted a retrospective, cross-sectional study on 1495 patients, with the majority consisting of THA and TKA patients (326 [21.0%] primary hips and 656 [42.2%] primary knees). The investigators diagnosed deep vein thromboses in 115 (7.5%) patients, pulmonary embolism in 163 (11.0%) patients, and deep vein thrombosis and pulmonary embolism in 27 (1.8%) patients.

According to the AAOS, this low rate of patients diagnosed with both deep vein thrombosis and pulmonary embolism calls into question the approach of using aggressive measures to treat deep vein thrombosis for the purpose of lowering the incidence of pulmonary embolism. Some investigators suggest that long-term anticoagulation with currently available agents be used judiciously to avoid bleeding disorders requiring blood transfusions or periprosthetic infections. Furthermore, AAOS claims that traditional anticoagulant drugs may be associated with higher all-cause mortality rates after THA and TKA.

However, the American College of Chest Physicians (ACCP) maintains that a consistent association between deep vein thrombosis and pulmonary embolism is demonstrated in imaging studies, as well as in the results of clinical trials that have shown a reduction of both deep vein thrombosis and pulmonary embolism with the use of anticoagulants vs placebo or untreated controls. The ACCP guidelines, which are based on results from randomized clinical trials and are widely used in THA and TKA, consider all patients undergoing THA and TKA to be at risk of venous thromboembolism and recommend the use of thromboprophylaxis with anticoagulants such as low-molecular-weight heparin or vitamin K antagonists in this population.

Some investigators have found asymptomatic distal deep vein thrombosis to be associated with an elevated risk of developing pulmonary embolism. In a series of studies by Pellegrini et al, investigators found that THA patients with asymptomatic calf deep vein thrombosis had an elevated risk of developing clinically significant pulmonary embolism within 8 weeks postoperatively. Of 174 patients, the 13 who received no anticoagulation at discharge were diagnosed with isolated deep vein calf thrombi by contrast venography within 7 to 10 days. Of these 13 patients, 4 (31%) subsequently developed pulmonary embolism. In another study, Pellegrini et al assumed that no pulmonary embolisms arose directly from deep calf thrombosis; they estimated that at least 1 in 5 fatal postoperative pulmonary embolisms resulted from untreated calf disease after THA.

Conclusion

Venous thromboembolism is a major health problem in the United States and can be associated with long-term morbidity. Therefore, thromboprophylaxis is not just for the prevention of pulmonary...
embolism, but also for venous thromboembolism prevention in general. Both symptomatic and asymptomatic deep vein thrombosis predispose patients to the development of recurrent venous thromboembolism, pulmonary embolism, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension, all of which are associated with reduced quality of life and substantial health care expenditures. Ongoing research is needed to further elucidate the causal relationship between deep vein thrombosis and pulmonary embolism.

The unique coagulation profiles of orthopedic surgery patients and procedures should be considered and further explored because currently available anticoagulation medications, such as vitamin K antagonists, are associated with a host of complications, particularly with long-term use. However, newer oral anticoagulants, such as direct thrombin inhibitors and Factor Xa inhibitors, show promise.

A greater understanding of the causes of deep vein thromboses and pulmonary embolisms and an awareness of the benefits and risks associated with newer agents will aid orthopedic surgeons in selecting optimal thromboprophylaxis to prevent deep vein thrombosis and pulmonary embolisms, both during hospitalization and after discharge.

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