Incidence of Deep Venous Thrombosis (DVT) Postoperatively Following Major Lower Limb Amputation in Patients on Prophylactic Anticoagulation

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Abstract

Background: Deep venous thrombosis (DVT) is part of a spectrum of venous thromboembolic disorders that includes superficial thrombophlebitis and pulmonary embolism. DVT may be defined as “the formation of a blood clot within a deep vein”. Although many studies have considered venous thromboembolism (VTE) in clinical and surgical patients, few have focused on patients who have undergone amputation of the lower extremities because of peripheral arterial disease (PAD). Few prospective research studies with a sufficiently large amputee patient sample have considered the incidence of deep venous thrombosis (DVT) in the early postoperative period. Data from existing studies are divergent, and the incidence of VTE is highly variable, ranging from 0% to 66.66%.

Aim of Study: The aim of this study is to prospectively document the incidence of DVT complicating major lower extremity amputation (above and below knee amputation) in patients using prophylactic anticoagulants.

Patients and Methods: The prospective study involved 35 patients underwent unilateral lower limb amputation. The mean age was 45±8.8 years (range: 18 to 55 years). They were 19 males (54.29%), and 16 females (45.71%), with ratio of 1.2: 1. Patients received prophylactic anticoagulant (Apixaban 2.5mg twice daily) immediately postoperatively and for 6 weeks, assessment after 3 & 6 weeks was done using duplex to exclude presence of DVT.

Results: There was no statistically significant difference between incidence of DVT and site of amputation, as 5/15 patients (33.3%) who underwent to BKA developed DVT, while 10/20 patients (50%) who underwent to AKA developed DVT (HR: 1.6 (95%CI: 0.4-6.5), p=0.487). Infection was associated with higher incidence of patients who developed post-operative DVT, as 11/15 patients (73.3%) had history of infection caused amputation, developed DVT, p-value = 0.002. Using venous duplex after 3 weeks from surgery, revealed that 9/15 patients (60%) who underwent AKA developed DVT, while 2/20 patients (10%) who underwent BKA developed DVT (p=0.001). Assessment after 6 weeks revealed that 3/20 patients (15%) who underwent BKA developed DVT, while 1/15 patient (6%) who underwent AKA developed DVT (p=0.6), with no statistically significant difference, thus emphasize that AKA was associated with early higher incidence of DVT rather than BKA.

Conclusion: DVT is a common complication following major lower limb amputation. And preoperative infection is considered main risk factor and increase risk of DVT. Occurrence of DVT is more in patients with AKA than others with BKA. Using prophylactic anticoagulants decrease risk of DVT up to 50%. And using of DOACs shows non-significant difference from other types of anticoagulants.

Key Words: Deep venous Thrombosis (DVT) – Major lower limb amputation – Prophylactic anticoagulation.

Introduction

DEEP venous thrombosis (DVT) is part of a spectrum of venous thromboembolic disorders that includes superficial thrombophlebitis and pulmonary embolism [1]. DVT may be defined as “the formation of a blood clot within a deep vein”. Although DVT most commonly occurs in the deep veins of the lower leg and thigh, it may also occur within the upper limb deep veins, visceral veins, and even the vena cava [2].

Venous thromboembolism is the third most common life-threatening cardiovascular disease, after myocardial infarction and stroke, in the United States [3]. According to the Centers for Disease Control and Prevention, the annual incidence of VTE is one or two per 1,000 persons, and the overall mortality rate is between 60,000 and 100,000 annually. One-half of patients with DVT will have long-term complications, including post-thrombotic syndrome and venous ulcers. One-third of patients with VTE will have a recurrence within 10 years [4].
Although many studies have considered venous thromboembolism (VTE) in clinical and surgical patients, few have focused on patients who have undergone amputation of the lower extremities because of peripheral arterial disease (PAD). Few prospective research studies with a sufficiently large amputee patient sample have considered the incidence of deep venous thrombosis (DVT) in the early postoperative period. Data from existing studies are divergent, and the incidence of VTE is highly variable, ranging from 0% to 66.66% [5].

Amputation involves considerable surgical trauma, including bone and soft tissue dissection and division, and many surgeons do not administer pharmacologic DVT prophylaxis because of concerns about bleeding complications. Studies of patients undergoing hip and knee prosthesis procedures show a high incidence of DVT, not only in the early postoperative period but also up to 30 days after surgery. Studies involving amputation of ischemic extremities have been limited to the hospitalization period and provide no data on the occurrence of DVT after discharge [5-7].

There are four main levels of major lower limb amputation: Below-knee (BKA), through-knee, above-knee (AKA), and through-hip. These four types of amputation have been shown to provide the best chance of using a prosthesis, which is why amputation is not performed directly at the level of the most distal viable tissue [8,9].

It is estimated that between 30 and 40 million people are living with total or partial limb loss in low-income countries internationally. The leading cause of amputation in these countries, and the second most common cause in the rest of the world, is severe traumatic injury [10].

The population of people with limb loss due to trauma is large, as they tend to be young with a long life expectancy [11]. Diabetes and vascular disease are associated with significant morbidity and mortality dysfunction [12].

In people with major amputates, blood clots are more likely to cause problems such as VTE. The risk of these events occurring is higher in people undergoing amputations. There are two forms of preventive measures for VTE: Drugs or compression devices. Drugs are effective in preventing VTE, but also have adverse side effects. Compression stockings or devices do not cause side effects, but are not suitable for everyone. Current guidelines of UK National Institute for Health and Care Excellence (NICE) recommend that any person undergoing an amputation of the lower limb should be offered drugs to prevent a blood clot. However, it is not clear which method is best for people having a lower limb amputation [13].

Patients and Methods

This prospective, interventional study involved thirty-five patients. The study was performed in the Faculty of Medicine, Ain Shams University and in El-SAHEL teaching hospital at the period from December 2021 to May 2022. Thirty-five patients included in this interventional study in which patients were recruited for need of major lower limb amputations for any possible cause. It is a single arm prospective clinical trial on role of anticoagulants in preventing of DVT in patients with major lower limb amputation. Patients were collected from the outpatient clinic, General Surgery Department, El-Demerdash Hospital, El Sahel Teaching Hospital and other authorized hospitals.

The study was conducted after approval of the protocol by the Local Research Committee & the Studies Committee as well as the Research Ethics Committee (IRB). An informed written consent was obtained from all patients before the study.

The included patients were over 18 years of age with normal hemoglobin level, platelet count, albumin level, coagulation profile, renal and liver function tests. Bed ridden patients with history of thromboembolic hereditary disorders, obese BMI >30kg/m², contraindications for anticoagulation therapy, surgery or anesthesia were excluded from the study.

Methods:

After personal and medical history and lab study, preoperative measure was done including patients’ assurance, nursing care for bed sores and pre-theatre checks include routine chest X-ray and electrocardiogram, full blood count, urea and electrolytes and blood glucose.

Planning for choosing the level of amputation, if AKA is performed, healing is more likely to occur, but this might be at the expense of the patient’s future mobility, since the knee joint is a vital structure in walking. For below-knee amputation (BKA), the stump must extend 11-12cm below the patella, and for AKA, it must be 22-28 cm below the tip of the greater trochanter to fit a functional prosthesis.

Assessment for the appropriate level of amputation involves clinical signs, such as the extent of necrosis, and potential function post-operatively.
A patient with a fixed contracture of the knee joint will not benefit from having a BKA as he or she will not be able to use an artificial limb. The stump wound in this case is unlikely to heal, as it is difficult to position the patient to avoid pressure on the stump when the knee is contracted.

Incisional stump pain in the first few days is usually controlled with an epidural infusion, patient-controlled analgesia pump or intermittent opiate analgesia. The patient should be encouraged to report any persistent or worsening stump pain, as it might be a sign of wound infection or continuing necrosis. Back pain is another common symptom after amputation, probably arising from the patient's changed posture and center of gravity. One measure that might be employed to relieve phantom pain is administration of oral Carbemazepine.

**Mangled extremity severity score:**

Mangled Extremity Severity Score (MESS) components prospectively collected in the Prospective Observational Vascular Injury Treatment (PROOVIT) registry [14].

The MESS was calculated for each patient by adding the numerical scores of the skeletal/soft tissue injury, limb ischemia, shock and age scores. If there were greater than 6 hours of ischemia time, the ischemia score was doubled [14].

**Statistical analysis:**

Data were analyzed with SPSS version 26. The normality of data was first tested with Shapiro-Wilk test. Qualitative data were described using number and percent. Continuous variables were presented as mean ± SD (standard deviation). The two groups were compared with Student t-test while paired t-test used to compare paired data. The results were considered: non-significant when the probability of error is more than 5% (p ≥ 0.05). Significant when the probability of error is less than 5% (p < 0.05). The smaller the p-value obtained, the more significant are the results.

**Results**

This prospective study involved 35 patients who underwent to unilateral lower limb amputation. The mean age of studied patients was 45 ± 8.8 years (range: 18 to 55 years). They were 19 males (54.29%) and 16 females (45.71%), with male to female ratio 1.2:1 (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categorical classification</th>
<th>No DVT (N=20/35)</th>
<th>DVT (N=15/35)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>10 (50%)</td>
<td>9 (40%)</td>
<td>0.5</td>
<td>1.5 (0.3,5.8)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10 (50%)</td>
<td>6 (40%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Above 40 y</td>
<td>14 (70%)</td>
<td>13 (86.7%)</td>
<td>0.2</td>
<td>2.7 (0.4,16.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Below 40 y</td>
<td>6 (30%)</td>
<td>2 (13.3%)</td>
<td>45 ± 8.8 years</td>
<td>47 (18-55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>9 (45%)</td>
<td>11 (73.3%)</td>
<td>0.8</td>
<td>1.1 (0.2,5.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11 (55%)</td>
<td>4 (26.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Below 25</td>
<td>17 (85%)</td>
<td>10 (66.7%)</td>
<td>0.1</td>
<td>2.8 (0.5,14.4)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Above 25</td>
<td>3 (15%)</td>
<td>5 (33.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td>28.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td></td>
<td></td>
<td></td>
<td>28 (26-35)</td>
<td></td>
</tr>
</tbody>
</table>

NS: Non significant. SD: Standard deviation.

These patients were received prophylactic anticoagulant (Apixaban 2.5mg twice daily) immediately post-operatively and for 6 weeks, assessment after 3 weeks and 6 weeks was done using duplex to exclude presence of DVT.

As regard to diseased venous segment, femoral vein thrombosis was associated with above knee amputation, while popliteal vein thrombosis was associated with below knee amputation (Table 3). Assessment of DVT presence after amputation was the primary endpoint for this prospective study, using venous duplex after 3 weeks from surgery, revealed that 9/15 patients (60%) who underwent AKA developed DVT, while 2/20 patients (10%) who underwent BKA developed DVT. p-value = 0.001. After 6 weeks; 3/20 patients (15%) who of
BKA developed DVT, while 1/15 patient (6%) of AKA developed DVT with no statistically significant difference ($p=0.6$), thus emphasize that AKA was associated with early higher incidence of DVT rather than BKA (Table 4).

Table (2): Incidence of DVT among patients either underwent to BKA or AKA.

<table>
<thead>
<tr>
<th>Surgery level</th>
<th>Incidence of DVT</th>
<th>HR (95% CI)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>BKA (%)</td>
<td>10 (45%)</td>
<td>5 (33.3%)</td>
<td>1.6 (0.4, 6.5)</td>
</tr>
<tr>
<td>AKA (%)</td>
<td>10 (55%)</td>
<td>10 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>20 (100%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Diseased venous segment with DVT and level of amputation.

<table>
<thead>
<tr>
<th>DVT Venous Segment</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>5</td>
<td>33.3%</td>
<td>4</td>
<td>20.0%</td>
<td>9</td>
<td>25.7%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>0</td>
<td>0.00%</td>
<td>5</td>
<td>25.0%</td>
<td>5</td>
<td>14.3%</td>
</tr>
<tr>
<td>Femoropopliteal</td>
<td>0</td>
<td>0.00%</td>
<td>1</td>
<td>5.00%</td>
<td>1</td>
<td>2.86%</td>
</tr>
<tr>
<td>Total DVT</td>
<td>10</td>
<td>66.6%</td>
<td>5</td>
<td>25.0%</td>
<td>15</td>
<td>42.8%</td>
</tr>
<tr>
<td>Without DVT</td>
<td>5</td>
<td>33.3%</td>
<td>15</td>
<td>75.0%</td>
<td>20</td>
<td>57.2%</td>
</tr>
</tbody>
</table>

DVT: Deep venous thrombosis.
AKA: Above knee amputation.
BKA: Below knee amputation.

Table (4): Incidence of DVT among AKA and BKA after 3 and 6 weeks from surgery.

<table>
<thead>
<tr>
<th>Incidence of DVT</th>
<th>AKA</th>
<th>BKA</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 3 w AKA</td>
<td>9/15 (60%)</td>
<td>2/20 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>After 6 w BKA</td>
<td>1/15 (6%)</td>
<td>3/20 (15%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Discussion

People undergoing major amputation of the lower limb are at increased risk of venous thromboembolism (VTE). Risk factors for VTE in amputees include advanced age, obesity, pre-operative infection, longstanding arterial disease and an identifiable hypercoagulable condition. Evidence suggests that pharmacological prophylaxis (e.g., heparin, factor Xa inhibitors, vitamin K antagonists, direct thrombin inhibitors, antplatelet) is effective in preventing deep vein thrombosis (DVT), but is associated with an increased risk of bleeding and wound complications [13].

This prospective study involved 35 patients underwent unilateral lower limb amputation. They received prophylactic anticoagulant (Apixaban 2.5mg twice daily) immediately postoperatively and for 6 weeks, assessment after 3 & 6 weeks was done using duplex to exclude presence of DVT.

A significant portion of studies have been conducted in people undergoing hip or knee replacement, including a Cochrane Review which found that extended-duration direct oral anticoagulants showed reduced symptomatic VTE and DVT [15].

Sometimes anticoagulant therapy fail to overcome postoperative thrombosis, Struijk-Mulder et al. [16] despite the fact that all patients in their study received pharmacological prophylaxis they found a high rate of pulmonary embolism. This could be explained by their study being the only one that screened for asymptomatic pulmonary embolism by means of ventilation-perfusion scanning. They believe that their findings are valid because they screened for both PE and DVT and they performed these examinations preoperatively as well as postoperatively.

In the current study, there was no statistically significant difference between incidence of DVT and site of amputation, as 5/15 patients (33.3%) who underwent to BKA developed DVT, while 10/20 patients (50%) who underwent to AKA, developed DVT [HR: 1.6 (95%CI: 0.4-6.5), $p=0.487$]. As regard to diseased venous segment, femoral vein thrombosis was associated with AKA, while popliteal vein thrombosis was associated with BKA.

Similar to our results, Yeager et al. [17] found no difference in the prevalence of DVT among their patients undergoing above-knee (4 of 31, 13%) compared with below knee amputation (5 of 41, 12%). However, they support the conclusion that DVT is often associated with lower extremity amputation.

In agreement with this study, Azeez et al. [18] stated that DVT in an amputated stump is more common following above knee amputation, as found in his report. Classical symptoms and signs of DVT are often absent which may lead to an underestimation of the problem [8]. Therefore, further examination of the patients with duplex scanning is often required to ascertain the diagnosis/
Assessment of DVT presence after amputation was the primary endpoint for this prospective study, using venous duplex after 3 weeks from surgery, revealed that 9/15 patients (60%) who underwent AKA developed DVT, while 2/20 patients (10%) who underwent BKA developed DVT ($p=0.001$). After 6 weeks revealed that 3/20 patients (15%) who underwent BKA developed DVT, while 1/15 patient (6%) who underwent AKA developed DVT ($p=0.6$), with no statistically significant difference, thus emphasize that AKA was associated with early higher incidence of DVT rather than BKA.

The high incidence of DVT in patients who underwent AKA is probably because the femoral vein is a conduction vessel with few tributaries, a feature that leads to poor venous flow in its remnant segments and consequent thrombosis. Old age (more than 70 years) was another factor related to DVT ipsilateral to the amputation, but no difference was observed in the distribution of AKA and BKA, or bedridden individuals [5].

The risk of VTE has been reported as ranging from 4.2% in the early postoperative period [17] to 28-50% 1 month after surgery [5,20] in lower extremity amputees not receiving thromboprophylaxis, although the number of patients studied was small. Other studies showed a lower incidence of 0-14% with different follow-up periods [21]. In these studies, not all patients received thromboprophylaxis.

O’Reilly et al. [22] described a series of 133 amputee patients who were followed over a two-year period. The study aimed to assess the utility of high-resolution ultrasound in the diagnosis of causes of pain in the stump. Eighty percent of amputations involved the lower limbs. The most frequent complications were the appearance of neuromas, followed by inflammation, soft-tissue calcifications, and other processes, such as infections or skin lesions. Venous thrombosis was among the less frequent lesions detected.

Uncertainty exists about the incidence of VTE after lower extremity amputation. Arterial thrombosis is the primary indication for amputation and is characterized by a cold, pale and atrophic leg. In venous thrombosis, however, there is precisely the opposite clinical image of a red, swollen and warm extremity. These symptoms are often absent in an amputation stump, which may lead to an underestimation of the problem. The absence of the muscles in the calf increases venous blood pooling and a decreased mobility may cause venous stasis and subsequent thrombosis [23]. The risk profile is further influenced by patient factors such as history of venous disease [17], thrombophilic abnormalities, obesity, (operation) trauma and a history of malignancy [24].

Limitations:

- No recent literatures published related to our title as we did not identify any eligible new studies for this update. There is a severe lack of evidence concerning the effectiveness of pharmacological and mechanical prophylaxis in the prevention of DVT in people with lower limb amputation.
- The relatively low number that interfere with the statistical analysis and accuracy of the results. The small number of patients also does not allow analysis of outcome in relation to indication for operation.

Conclusion:

DVT is a common complication following major lower limb amputation. And preoperative infection is considered main risk factor and increase risk of DVT. Occurrence of DVT is more in patients with AKA than others with BKA. Using prophylactic anticoagulants decrease risk of DVT up to 50%. And using of DOACs shows non-significant difference from other types of anticoagulants.

References


معدلات حدوث الإصابة بجلطات الأردية العميقه بعد جراحات بتر الأطراف السفلية الرئيسية في المرضى الذين يخضعون لمضادات التجلط الوقائية

يوفر بتر الأطراف السفلية التي تتراوح عن بتر بأصابع القدم حتى بتر على مستوى مفصل الركبة مجموعة متنوعة من خيارات العلاج لعديد من الأمراض بما في ذلك تزويد الأطراف العشريّة والسدة الأمامية. وكثيراً ما يتم إجراء بتر فوق الركبة وتر أسفل الركبة مما يؤدي بشكل كبير على حياة المريض.

ويتيح فهم المبادئ الأساسية إمكانية التنبؤ بشكل أفضل بالمستوى الصحيح للبر للمرضى، مع الحفاظ على الحد الأقصى من الوظائف التي يمكن تقديمها. توجد العديد من الفروض التنبؤية أدلة أكبر والسماح بتقييم الأعراض. يفضل بتر الأطراف السفلية، بخلاف الإصابة بجلطات الأردية العميقة إلى 50%.

هدف هذه الدراسة هو رصد معدلات حدوث الإصابة بجلطات الأردية العميقة بعد جراحات بتر الأطراف السفلية (سواء فوق أو أسفل مستوي مفصل الركبة) في المرضى الذين يخضعون لمضادات التجلط الوقائية.

شملت هذه الدراسة 25 مرضاً خضعوا لبر الأطراف السفلية بجانب واحد كجزء من توسعة العمر 88±8 سنة (المدى من 18 إلى 55 سنة). و كانوا ذكور (9/24) و إناثاً (16/76) بنسبة (1:2.4).

تتلقى المرضى مضادات التجلط (إيبكسابان جرعة الوقائية 6.5 مجم مرتين يومياً) مباشرة بعد الجراحة و لمدة 6 أسابيع. والتقيم بعد 2 و 6 أسابيع باستخدام جهاز محمدات فوق الصوتية (الديسك) لاستخدام جلثقات الأرديه العميقة.

تعد الإصابة بجلطات الأردية العميقه من المضاعفات الشائعة بعد جراحات بتر الأطراف السفلية الرئيسية وتتعرض المرضى قبل إجراء الجراحة عامل رئيسي و يزيد من خطر الإصابة بجلطات الأرديه العميقه.

تتضمن الإصابة بجلطات الأردية العميقه في المرضى الذين يخضعون لبر فوق مستوي الركبة أكثر من غيرهم الذين يخضعون للبر أسفل مستوى الركبة.

يقلل استخدام مضادات التجلط الوقائية من خطر الإصابة بجلطات الأردية العميقه بنسبة تصل إلى 50%.

ويظهر استخدام مضادات التجلط ارتجاء من طريق الفحص تقدير طيف عن غيرها من مضادات التجلط في نسب حدوث جلطات الأردية العميقه بعد جراحات بتر الأطراف السفلية الرئيسية.