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Deep vein thrombosis associated with major lower extremity amputation

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Abstract: Background: Patients undergoing lower extremity amputation are potentially at high risk for thromboembolic complications. Immobility and surgically induced venous endothelial trauma may predispose the patient undergoing amputation to development of lower extremity deep vein thrombosis. In spite of the perception that lower extremity amputation is associated with thromboembolic complications, limited data are available documenting the prevalence of DVT after amputation. **Aim of the Work:** to prospectively document the incidence of DVT complicating lower extremity amputation. **Patients and Methods:** After obtaining approval from the ethical committee, this prospective and descriptive study included 62 amputations in 56 patients admitted consecutively to the Emergency Department and the Vascular Surgery Ward of the Demerdash Hospital of the Faculty of Medicine of Ain Shams University, Egypt, was conducted from January 2019 through July 2019. The mean age of the patients was 67.25, 11.7 years (range, 43-88 years), and 51.7% were men. **Results:** During recovery, 16 cases of DVT were diagnosed in the ipsilateral amputated extremity, 12 within the first 5 days (75%) and four after this period. Of the 16 cases, 14 (87.5%) were diagnosed during outpatient care The cumulative incidence of DVT ipsilateral to the amputation was 24.4% 3 days and 28.0% 5 days, with respective standard errors of 0.057 and 0.064. **Conclusion:** The incidence of DVT ipsilateral to the amputation is elevated during the early postoperative period (5 days), mainly in AKA and at ages of 70 years. There was no relationship between the presence of the other comorbidities studied and postoperative DVT occurrence. All patients with PAD scheduled to undergo major amputation should be considered at high risk for the development of DVT, even during the period after discharge from the hospital. On the basis of these results, we recommend prophylactic anticoagulation (if not contraindicated) and surveillance to all patients undergoing this type of procedure. Further studies are required to determine the optimal method and duration for prophylaxis treatment.

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1. Introduction

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common lethal disorder that affects hospitalized and nonhospitalized patients, is often overlooked, and results in long-term complications including chronic thromboembolic pulmonary hypertension (CTPH) and the post-thrombotic syndrome (PTS) [(1)].

Venous thromboembolism results from a combination of hereditary and acquired risk factors, also known as thrombophilia or hypercoagulable states. In addition, vessel wall damage, venous stasis, and increased activation of clotting factors first described by Rudolf Virchow more than a century ago remain the fundamental basis for our understanding of thrombosis [(2)].

Venous thromboembolism is the third most common cardiovascular illness after acute coronary syndrome and stroke. Although the exact incidence of VTE is unknown. Pulmonary embolism is the third most common cause of hospital-related death and the most common preventable cause of hospital-related death [(3)].

In the EU, It has been noted that VTE is responsible for more than twice the number of deaths than those caused by AIDS, breast cancer, prostate cancer and road traffic accidents combined [(4)].

VTE can lead to serious long-term complications, including post-thrombotic syndrome (PTS) and thrombo-embolic pulmonary hypertension (CTPH). PTS is the most common complication of DVT and typically causes chronic pain and swelling in the affected leg, and in severe cases can result in venous ulcers. After symptomatic DVT, 20–50% of patients develop PTS [(5)].

CTEPH is a serious long-term complication of PE, but it can be difficult to diagnose because clinical symptoms and signs are non-specific or absent in early CTEPH. Many of the symptoms are similar to those

for acute PE, including dyspnoea, chestpain, presyncope or syncope and/or haemoptysis. CTEPH causes the right side of the heart to work harder than normal owing to abnormally high blood pressure in the arteries of the lungs. This can lead to heart failure and other serious consequences [(3)].

The clinical examination of DVT is often unreliable; therefore, clinical decision rules (pretest probability scores) based on the patient's signs, symptoms, and risk factors have been developed to stratify patients into low, moderate, or high clinical probability. This approach helps to improve the effectiveness of diagnosing DVT and to limit the need for additional testing. Using a clinical decision rule patients in the low pretest probability category have a 96% negative predictive value for DVT (99% if the D dimer is negative as well).

The positive predictive value in patients with a high pretest probability is less than 75%, supporting the need for further diagnostic testing to identify patients with an acute thrombosis.17-20 A clinical prediction score has also been developed for upper extremity DVT using the presence of a pacemaker or a catheter or access device in the internal jugular or subclavian veins, localized pain, unilateral pitting edema, or another diagnosis at least as plausible as independent predictors for DVT [(6)].

The main goals of treatment for DVT include prevention of PE, the PTS, and recurrent thrombosis. Once VTE is suspected, anticoagulation should be started immediately unless there is a contraindication. Different types of anticoagulant can be used including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux followed by an oral anticoagulant (vitamin K antagonist [VKA]), Direct thrombin inhibitors [(7)].

Aim of the Work

The aim of this work is to discuss different types of anticoagulants with different duration for treatment of venous thromboembolic patients.

2. Patients and Methods

A prospective and descriptive study of patients admitted consecutively to the Emergency Department and the Vascular Surgery Ward of the Demerdash Hospital of the Faculty of Medicine of Ain Shams University, Egypt, was conducted from January 2019 through July 2019. The study was reviewed and approved by the local Research Ethics Committee.

The following variables were studied: age, sex, heart disease, smoking, bedridden status, female hormone therapy, obesity (body mass index 30 kg/m^2), systemic arterial hypertension, diabetes mellitus, chronic renal failure, varicose veins of the lower extremities, paresthesia or paraplegia of the limbs, malignancy, level of arterial occlusion, secondary infection of the ischemic extremity, and recent arterial revascularization surgery. We analyzed the association between the incidence of VTE and the level of amputation, general medical postoperative complications, amputation stump complications, and postoperative mortality.

The accuracy of each patient's history and clinical examination was tested, comparing the data with color-flow Doppler findings, and checking clinical examination sensitivity and specificity.

Duplex ultrasound (DUS) scanning was chosen as the diagnostic method for DVT due to its noninvasive characteristic and ability to provide reproducible results in repeated examinations,[11] as well as its high sensitivity in examining the proximal deep venous system of the lower extremity.[12-14] Patients underwent DUS imaging once before amputation and twice after surgery, between postoperative days 3 and 5.

All patients received acetylsalicylic acid (100 mg, daily) preoperatively and postoperatively, but none received prophylactic anticoagulation. DVT were treated with nonfractionated heparin or low molecular-weight heparin, followed by warfarin sodium for a period of 6 months.

All patients investigated in the study presented with chronic arterial obstruction of the lower extremities, with or without previous arterial revascularization, and were indicated for above knee amputation (AKA) or below knee amputation (BKA). Patients who received any type of anticoagulation therapy before surgery or who were unwilling to participate in the study were not included. The treatment regimen in patients excluded due to previous anticoagulation was not discontinued.

Patients were excluded from the study if (1) DVT was identified during the preoperative or intraoperative period (all divided veins were assessed for the presence of intraluminal thrombi and the findings were reported by the surgeon), (2) the postoperative DUS scan was not performed for any reason, (3) DVT was diagnosed only in the contralateral extremity during the postoperative period.

Table I. Prevalence of associated diseases (n 60)

Disease	*No. (%)*
Systemic arterial hypertension	48 (80.0)
Diabetes mellitus	42 (70.0)
Heart disease	16 (26.7)
Varicose veins of lower limbs	14 (23.3)
Cerebral vascular accident	13 (21.7)
Obesity	7 (11.7)

Statistical analysis.

The cumulative incidence of DVT of the stump and mortality were determined by the Kaplan Meier method, with an accepted standard error of up to 0.1. Univariate analysis of the risk factors for DVT was obtained by the log-rank test method, and Cox regression was applied for multivariate analysis. Statistical significance was set at *P*.05.

Results

The predominant location of obstructive arterial disease in the amputated limb was the femoropopliteal segment (71%). The prevalence of both iliofemoral and infra.

The *arrowhead* indicates the average day of discharge after amputation. popliteal disease was 14.5%. The most frequent level of amputation was BKA, in 36 (58.1%) cases. The left lower extremity was the site of amputation in 51.6%. None of the patients underwent knee disarticulation.

Medical complications occurred in 20.0% of the patients as follows: bronchopneumonia in 11.7%, peritonitis and acute myocardial infarction in 3.3% each, and sepsis in 1.7%. One patient (1.6%) presented with a symptomatic nonfatal PE. Amputation stump complications occurred in 45.3% of the amputations. In five cases of BKA, an early (30 days) more proximal amputation was necessary.

During recovery, 16 cases of DVT were diagnosed in the ipsilateral amputated extremity (Table III), 12 within the first 5 days (75%) and four after this period. Of the 16 cases, 14 (87.5%) were diagnosed during outpatient care, the average time to discharge after amputation was 6.11 days (range, 1-56 days). No iliac DVT was diagnosed, and none of the patients who underwent bilateral amputation had evidence of DVT. DVT also occurred in the contralateral limb in three patients. The cumulative incidence of DVT ipsilateral to the amputation was 24.4% 3 days and 28.0% 5 days, with respective standard errors of 0.057 and 0.064 (Fig 1).

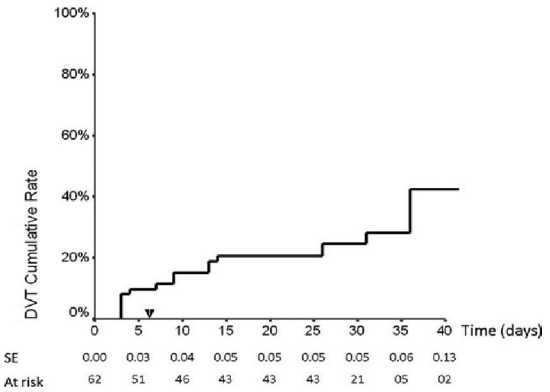

Fig 1. Cumulative incidence of venous thrombosis of the amputation stump by the Kaplan-Meier method.

Table (II): Univariate analysis of risk factors for deep venous thrombosis of the amputation stump (log rank)

Factor	*No.*	*DVT per 100 individuals/d*	*Rate of events*	P
Sex Male	31	1.506	1	.13
Female	31	0.725	0.48	
Arterial hypertension Yes	50	1.063	0.95	.89
No	12	1.115	1	
Diabetes mellitus Yes	44	0.810	0.44	.09
No	18	1.837	1	
Smokers Yes	13	0.929	0.84	.69
No	49	1.112	1	
Bedridden Yes	39	0.819	0.53	.20
No	23	1.557	0	
Amputation level Thigh	26	1.792	1	.044
Leg	36	0.643	0.36	
Age, y 69	36	0.590	0.28	.012
70	26	2.105	1	
Side Left	32	0.960	0.81	.55
Right	30	1.180	1	
Obesity Yes	8	0.885	0.62	.66
No	54	1.419	1	
Ischemia/limb infection Yes	48	1.025	0.83	.76
No	14	1.242	1	

Factor	*No.*	*DVT per 100 individuals/d*	*Rate of events*	P
Reamputation Yes	5	2.273	1	.66
No	57	1.036	0.46	
Contralateral amputation Yes	6	1.460	1	.67
No	56	1.033	0.71	
Stroke Yes	14	1.163	1	.94
No	48	1.045	0.90	
Heart disease Yes	17	1.626	1	.37
No	45	0.890	0.55	
Revascularization Yes	8	1.031	0.96	.99
No	54	1.078	1	
Stump complications Yes	27	1.250	1	.67
No	35	0.939	0.75	
Clinical complications Yes	11	0.725	0.63	.44
No	51	1.151	1	
Death Yes	6	3.278	1	.20
No	56	0.978	0.3	
Varicose veins Yes	15	1.312	1	.72
No	47	0.990	0.75	

DVT, Deep venous thrombosis.

Clinical evaluation of the signs and symptoms of DVT in the amputated limb had sensitivity of 56.2%, specificity 82.6%, negative-predictive value of 84.4%, and a positive predictive value of 52.9%.

Univariate analysis (Table 2) demonstrated a significant difference in the incidence of DVT ipsilateral to the amputation when different levels were compared. AKA presented a cumulative incidence of venous thrombosis of 37.5%, compared with 21.2% in patients who underwent BKA, within the period up to day 35 after surgery (*P*.04).

Patients aged 70 years had significantly higher risk for DVT in the amputated limb than younger patients within the 5 day period (48.9% vs 16.8%, respectively; *P*.012). The multivariate analysis showed no association between risk factors and the occurrence of DVT in the amputated extremity.

Discussion

Analysis of the general patient characteristics revealed no difference in the indications for amputation and complications in the amputated extremity with regard to previous related data [(8)]. The most frequent site of chronic arterial occlusion in this investigation was the superficial femoral artery, in accordance with ***Roon et al.*** [(9)]. The percentage of patients who had undergone recent prior revascularization of the amputated limb was within the limits found in the literature [(10)]. We also observed that the concomitant bilateral amputations were in accordance with other reports that stated values of 10.68% to 15% [(11)].

Previous studies [(12)] reported that failed BKA occurs in approximately 15% of patients, similar to the incidence observed in the present study. All new amputations to a more proximal level were performed in the BKA group. BKA failure was probably related to the surgery being performed distal to a femoropopliteal obstruction (absence of a palpable popliteal pulse) and close to an infection source. Most patients had combined ischemia and local infection preoperatively; these are contributing factors for infection as the major cause of BKA complication (54.5%). The occurrence of these complications and new amputation to a more proximal level did not influence the incidence of DVT.

Previous studies report that the incidence of nonfatal symptomatic PE varies from 2.1% to 8% [(11)]. We believe that the low incidence of symptomatic PE in the present study was due to the diagnostic accuracy of the DUS series, which resulted in immediate treatment of DVT and a consequent decrease in the incidence of PE. Another possible reason was our choice not to investigate patients without pulmonary symptoms. When diagnostic examinations were performed for routine asymptomatic PE in previous studies, results varied from 11% to 14.28% [(13)]. Although the study by Williams et al[34] attributed a PE risk four times higher for amputations at the AKA level, we had no cases of PE for AKA amputation in our study and only one PE in a BKA.

Previous reports described perioperative mortality for major amputation varying from 0% to 37% [(14)]. We also observed a mortality rate within this

range. Univariate statistical analysis revealed no relationship between DVT and death. Nearly all DVT was diagnosed in the first 5 days after surgery, in agreement with previous studies, independent of sample and methodology used [15].

The patients who required amputation were not solely at risk in the early postoperative period, they were also at risk after hospital discharge. In this study, 87.5% of the DVT diagnoses were made at the scheduled outpatient return appointment for the postoperative DUS examination. This finding differs from that of others studies because most researchers have studied the incidence of DVT only during the hospitalization [16].

A relationship was found between the type of amputation performed and the incidence of DVT. 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 (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.

The presence of the other studied risk factors and variables showed no relation to DVT ipsilateral to the amputation, even after multivariate analysis; this finding is in contrast to data from previous studies for clinical and surgical patients in general [17]. This discrepancy may reflect the relatively small number of patients in the present study.

Yager et al. [15] demonstrated DVT risk factors to be chronic venous insufficiency or previous history of DVT, or both, and the presence of prior amputation of the contralateral extremity. Their analysis also included patients diagnosed in the preoperative period (6 of 9, 66.7%) and in the contralateral limb (4 of 9, 44.4%), and was conducted using a methodology distinct from that used in our study, in which we only considered postoperative cases of DVT in the amputated extremity stump.

The incidence of DVT ipsilateral to the amputation is elevated during the early postoperative period (5 days), mainly in AKA and at ages of 70 years. There was no relationship between the presence of the other comorbidities studied and postoperative DVT occurrence. All patients with PAD scheduled to undergo major amputation should be considered at high risk for the development of DVT, even during the period after discharge from the hospital. On the basis of these results, we recommend prophylactic anticoagulation (if not contraindicated) and surveillance to all patients undergoing this type of procedure. Further studies are required to determine the optimal method and duration for prophylaxis treatment.

Conclusion:

The incidence of DVT ipsilateral to the amputation is elevated during the early postoperative period (5 days), mainly in AKA and at ages of 70 years. There was no relationship between the presence of the other comorbidities studied and postoperative DVT occurrence. All patients with PAD scheduled to undergo major amputation should be considered at high risk for the development of DVT, even during the period after discharge from the hospital. On the basis of these results, we recommend prophylactic anticoagulation (if not contraindicated) and surveillance to all patients undergoing this type of procedure. Further studies are required to determine the optimal method and duration for prophylaxis treatment.

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