

# Risk factors for deep vein thrombosis in surgical patients

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**Abstract.** Objective: This study investigates the risk factors for developing deep vein thrombosis (DVT) of the lower limbs one month after general surgery. Material and methods: The study included 196 patients (112 (57.1%) women and 84 (42.9%) men) who underwent surgery. Median age was 62 (44; 71) years. The diagnosis of acute DVT of the lower limbs was excluded in these subjects, before surgery, by duplex ultrasonography. All patients underwent ultrasound examination one month after surgery. We noted several clinical, demographic and lab parameters known to be associated with DVT. Results: The incidence of DVT was diagnosed in 4 (2%) patients one month after surgery. In our study, patients heterozygous for the factor V Leiden mutation had the highest risk for developing acute DVT of the lower limbs (OR, 35). Personal history of DVT was the second risk factor, in terms of importance, for the incidence of DVT after surgery (OR, 9.2). The presence of varices was another parameter that increased the risk of DVT in patients undergoing surgery (OR, 8.6). Conclusion: The incidence of acute DVT of the lower limbs one month after surgery was of 2%. Factor V Leiden was the most important parameter associated with an increased risk of acute DVT. Personal history of DVT was a risk factor for postoperative DVT. Varicose veins were associated with the incidence of postoperative DVT.

**Key Words:** deep vein thrombosis, surgery, risk factors.

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## Introduction

Venous thromboembolism is a common cause of preventable hospital mortality. In the USA, about 30% of the 200,000 deaths related to venous thromboembolism occur after surgery (Horlander et al 2003).

Each surgical patient has a specific risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE), so it is necessary to quantify this risk before surgery in order to try to prevent it by means of specific drug and/or mechanical prophylaxis. In most cases, perioperative DVT develops in the deep veins or muscle veins of the lower leg (calf) and thrombi usually originate in the valve cusps (Nicolaidis et al 1971). Approximately 50% of all cases of calf deep vein thrombosis are self-limiting and resolve within the first 72 hours after surgery, 40% remain in the calf, and 10% progress to proximal vein thrombosis, which greatly increases the risk of PE (Kakkar et al 1969). Venous thrombosis associated with surgery occurs exactly during surgery, but mostly develop within days, weeks or even months after the event (Maynard et al 1991).

The risk of progression of postoperative DVT is additive to that given by other risk factors, particularly immobilization, malignancy and thrombophilia. The risk of DVT is different depending on the type of surgery performed. Surgical interventions such as laparoscopic cholecystectomy, appendectomy, transurethral prostatectomy or mastectomy have the lowest risk of developing DVT (Gould et al 2012). General surgery has a 15-30%

risk of developing DVT in the absence of anticoagulant or mechanical prophylaxis. Vascular surgery may be complicated with venous thrombosis in up to 30% of cases, this percentage being reduced to 2.8% in case of drug prophylaxis (Geerts et al 2008). Orthopedic surgery and surgery performed in patients with multiple injuries have the greatest risk of developing DVT (Gould et al 2012).

DVT occurring after general surgery is a common pathology in the absence of specific prophylaxis with significant morbidity and mortality and high socioeconomic costs.

This study investigates the risk factors for developing DVT of the lower limbs one month after general surgery.

## Materials and methods

This was an observational, prospective, analytical, longitudinal, cohort study.

The study included 196 patients (112 (57.1%) women and 84 (42.9%) men) who underwent surgery. Median age was 62 (44; 71) years. The diagnosis of acute DVT of the lower limbs was excluded in these subjects, before surgery, by duplex ultrasonography. All patients with no signs of DVT underwent ultrasound examination one month after surgery. Those who experienced specific symptoms of DVT of the lower limbs (edema, pain, erythema, local hyperthermia, endured venous cord) underwent clinical and ultrasound examination before the one month visit.

Patients were selected from those admitted to the surgical unit of Municipal Clinical Hospital of Cluj-Napoca between December 2011 and June 2012.

Subjects were included in the study after signing an informed consent form for inclusion in the study and genetic determinations. The study protocol was approved by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.

### Inclusion criteria

Patients over 18 years old, who were about to undergo surgery, were enrolled in the study after signing the informed consent form. Duplex ultrasonography was performed using an Aloka SSD 4000 unit, equipped with a linear transducer with variable frequency ranging between 7 and 10 MHz and with a sector transducer with variable frequency between 2.5 and 6 MHz.

Ultrasonographic diagnosis of acute DVT was established by using B mode (brightness mode) ultrasound, color and pulsed Doppler echocardiography, which revealed the presence of major or minor, direct or indirect signs: homogeneous material, echogenic in the examined vein (direct major signs), incompressible character of the examined vein (indirect major sign), distension of the examined vein compared to contralateral vessel (minor sign), lack of venous flow augmentation during calf or thigh distal compression (minor sign) (Torbicki et al 2008).

### Exclusion criteria

Patients receiving oral or injectable anticoagulant therapy before admission were not included in the study. Patients who had ultrasound evidence of the presence of acute DVT of the lower limbs were also not included in the study.

### Quantified variables

General (age, gender, area of origin), clinical and laboratory data were recorded for each patient.

From patient history and clinical examination we noted data regarding the presence of comorbidities or different circumstances that could have increased the risk of acute DVT: chronic obstructive pulmonary disease, high blood pressure, heart failure, cancer, cerebrovascular accident, history of DVT or PE, bed rest for more than three days, major surgery in the last month, fractures of legs or pelvis in the last month, autoimmune or infectious diseases, flights or car trips lasting more than 4 hours in the last month, varicose veins of the lower limbs and local trauma. The presence/absence of concomitant chemotherapy was also noted. Body mass index (BMI) was calculated for each patient: normal < 25 kg/m<sup>2</sup>, overweight - BMI between 25 and 30 kg/m<sup>2</sup>, grade 1 obesity - BMI between 30.1 and 34.9 kg/m<sup>2</sup>; grade 2 obesity - BMI between 35 and 40 kg/m<sup>2</sup>, grade 3 obesity - BMI > 40 kg/m<sup>2</sup>.

The type of anesthesia, the duration of surgery, the duration of postoperative immobilization, the use of anticoagulant prophylaxis and its duration were noted from the data related to the surgical procedure performed.

Three milliliters of venous blood were collected from each patient in a vacutainer containing EDTA. DNA was obtained from the blood sample at the Department of Genetics of the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, using a DNA extraction kit (Wizard Genomic DNA Purification Kit, Promega, Madison, WI, USA).

### Determination of genotypes

Genotyping of factor V Leiden mutation (g.1691 G>A; p.Arg506Gln) was adapted by means of a PCR-RFLP protocol originally described by Bertina et al in 1994.

Genotyping of prothrombin G20210A mutation was adapted by means of a PCR-RFLP protocol originally described by Ferraresi et al in 1997.

Genotyping of the MTHFR (Methylene tetrahydrofolate reductase) C677T polymorphism was adapted by means of a PCR-RFLP protocol initially described by Zhou-Cun et al in 2007.

For MTHFR A1298C polymorphism genotyping we developed an ARMS-PCR (Amplification Refractory Mutations System - Polymerase Chain Reaction) protocol which is based on selective amplification of the normal and the mutant allele in two different reactions using two specific primers for the normal allele, respectively the mutant allele, and a common primer for both alleles.

The amplification program for both alleles consists of: initial denaturation for 10 minutes at 950C, followed by 30 cycles, each consisting of 30 sec denaturation at 950C, 20 sec heating at 570C and 20 sec elongation at 720C, and finally, a 7 minute elongation. The sequences of the primers used are as follows: FwN\_5'-CGAAGACTTCAAAGACACTTT-3', FwM\_5'-CGAAGACTTCAAAGACACTTG-3', RevC\_5'-TCTTTGTTCTTGGGAGCGG-3'.

### Statistical analysis

For statistical analysis we used MedCalc 12.7 software. Data were classified as nominal categorical and quantitative. For the description of nominal and categorical variables we calculated frequencies and percentages. For quantitative variables we used the mean  $\pm$  standard deviation or the median and the 25th and 75th percentiles, according to distribution for normality tested by the Kolmogorov-Smirnov test. Percentage differences between nominal and categorical variables were calculated using Fisher's exact test. To highlight the differences of a quantitative variable between two categories we used the Mann-Whitney test. A p-value of 0.05 was chosen as statistical significance threshold.

## Results

The incidence of DVT was diagnosed in 4 (2%) patients one month after surgery. Clinical and demographic characteristics as well as paraclinical characteristics of subjects in the group can be seen in Table 1.

For the risk of developing DVT in patients who have revealed the existence of factor V Leiden, we calculated an OR of 35, CI95% 3.4-361.5.

For the risk of DVT in patients with varicose veins of the lower limbs, we calculated an OR of 8.6, CI95% 1.1-64.4.

For each one minute increase in surgical time we determined a 1.02-fold increase in the risk of DVT, CI95% 0.9-1.04

The history of DVT enhanced the risk of a new DVT by 9.2 times (CI95% 0.9-91.1).

## Discussions

This study assessed the potential of several parameters to be risk factors contributing to the occurrence of acute DVT of the lower limbs one month after general surgery.

Table 1. Clinical characteristics and comorbidities of patients in the DVT group and in the control group.

Variable	with DVT	without DVT	p
<b>Patients</b>	4	194	-
<b>Age (years)</b>	35 (22.2; 62)	63 (53.75; 72)	0.09
<b>Men</b>	1 (25%)	83 (43.2%)	0.6
<b>Women</b>	3 (75%)	109 (56.8%)	
<b>History of DVT</b>	3 (75%)	1(25%)	0.05
<b>Cancers</b>	0 (0%)	4 (100%)	1**
<b>Obesity</b>	<b>0</b>	2 (50%)	0.07
	<b>I</b>	1 (25%)	
	<b>II</b>	0 (0%)	
	<b>III</b>	1 (25%)	
<b>Trip &gt; 4 hours</b>	0(0%)	4 (100%)	1
<b>Varices</b>	3 (75%)	1 (25%)	0.05
<b>Smoking</b>	0 (0%)	4 (100%)	1
<b>Anesthesia</b>	<b>Spinal</b>	0 (0%)	0.3
	<b>General</b>	4 (100%)	
<b>Injectable anticoagulant prophylaxis</b>	2 (50%)	2 (50%)	1
<b>Duration of anticoagulant prophylaxis</b>	1±1.1	1.8±2.5	0.7
<b>Duration of surgery (minutes)</b>	105 (67.5; 142.5)	60 (30; 90)	0.04
<b>Factor V Leiden</b>	3 (75%)	1 (25%)	0.002
<b>Prothrombin G20210A</b>	0 (0%)	4 (100%)	1
<b>MTHFR C677T</b>	<b>wild type</b>	2 (50%)	0.7**
	<b>heterozygous</b>	2 (50%)	
	<b>homozygous</b>	0 (0%)	
<b>MTHFR A1298C</b>	<b>wild type</b>	1 (25%)	0.3**
	<b>heterozygous</b>	3 (75%)	
	<b>homozygous</b>	0 (0%)	

Aside from the fact that PE is the first cause of preventable hospital mortality and that most of these episodes are due to DVT, there is also the economic aspect of venous disease prophylaxis that should be considered. Non-pharmacological means of prevention after surgery, such as stockings or intermittent pneumatic compression, have saved 32 lives and reduced costs by nearly 800,000 dollars in 10,000 treated patients in comparison to those who did not apply any kind of prophylaxis. Prophylaxis with unfractionated heparin therapy saves 7 more patients and determines higher costs by 568,000 dollars in 10,000 patients (Oster et al 1987). Low molecular weight heparins were even more effective than unfractionated heparin in the prevention of postoperative DVT, and they even generated slightly lower costs than the latter (Szucs et al 1999). The conditions that increase

the risk of DVT the most after surgery should be thoroughly known in order to efficiently implement thromboprophylaxis. Our research revealed the occurrence of acute DVT of the lower limbs one month after surgery in 4 (2%) patients. Literature data show a 1.5% incidence of DVT in general surgery in those with low risk of DVT, a 3% incidence in those with moderate risk and 6% in those with high risk. From this point of view, the incidence of DVT in our study shows the existence of a low/medium risk in study patients. There was no significant difference in percentage between patients with thromboprophylaxis who developed DVT and those without thromboprophylaxis who also revealed DVT. This demonstrates that some patients who were at low risk of developing DVT and did not receive injectable anticoagulants, presented unknown risk factors, most likely thrombophilia or neoplasms, which resulted in the occurrence of DVT. At the same time, there have been patients with medium/high risk of developing DVT, who, in spite of correctly receiving anticoagulant prophylaxis, developed DVT, probably also due to hidden factors that have greatly elevated the risk of thrombosis.

In our study, patients heterozygous for the factor V Leiden mutation had the highest risk for developing acute DVT of the lower limbs. Factor V Leiden mutation is a point mutation in factor V gene which is obtained by the substitution of adenine for guanine at nucleotide position 1691. After substitution, factor V Q506 or factor V Leiden occurs. Activated protein C resistance occurs because factor V Leiden is inactivated more slowly than the normal one (Van Der Meer et al 1997). There is a 4 to 12% prevalence of heterozygous subjects for factor V Leiden mutation (Herrmann et al 1997). In our study, there was a 9% prevalence which was consistent with the limit reported by literature data. Several studies in the literature have shown that factor V Leiden is associated with an increased incidence of DVT after surgery (Lowe et al 1999; Edmonds et al 2004). Personal history of DVT was the next risk factor, in terms of importance, for the incidence of DVT after surgery. Approximately 75% of patients who were diagnosed with DVT had personal history of thrombosis. Studies and meta-analyzes in the literature also show that previous thrombosis is a strong predictive marker for the occurrence of other postoperative DVT (Clarke-Pearson et al 1987; Greer & De Swiet 1993).

The presence of varices was another parameter that increased the risk of DVT in patients undergoing surgery. The role of varicose veins in the appearance of postoperative DVT is not clear. Venous stasis due to varicose veins is probably the only explanation of their role in DVT. Lowe et al (1993), Heit et al (2000) and Clarke-Pearson et al (1987) have demonstrated the association between varicose veins and postoperative DVT.

Some limitations of the study may include: the relatively short follow-up of patients, single-center trial and the relatively small number of patients.

## Conclusion

The incidence of acute DVT of the lower limbs one month after surgery was of 2%. Factor V Leiden was the most important parameter associated with an increased risk of acute DVT. Personal history of DVT was a risk factor for postoperative DVT. Varicose veins were associated with the incidence of postoperative DVT.

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**Citation** Pop, T. R., Crișan, S., Chirilă, D. N., Buzoianu, A. D., 2013. Risk factors for deep vein thrombosis in surgical patients. *HVM Bioflux* 5(3):99-102.

**Editor** Ștefan C. Vesa

**Received** 10 September 2013

**Accepted** 15 October 2013

**Published Online** 19 October 2013

**Funding** None reported

**Conflicts/  
Competing  
Interests** None reported