ANTICOAGULATION IN THE INTENSIVE CARE UNITS

Essay

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Abstract

Venous thromboembolism (VTE) remains a significant cause of morbidity and mortality. Untreated DVT may lead to long-term morbidity because of post thrombotic syndrome, recurrent VTE and pulmonary embolism.

The identification of patient risk factors for VTE and careful consideration of the risks and the benefits associated with available therapeutic options provide the basis for the appropriate use and selection of prophylactic therapy in this patient population. Different therapies used for thromboprophylaxis in the medically ill patients are discussed. The use of anticoagulants in pediatric patients can be challenging, because these patients have physiological differences that needs special modifications. Management of Bleeding caused by misusing anticoagulants or as a side effect is addressed. New therapies and evolving drugs used for VTE prophylaxis are approached.

Key words
ANTICOAGULATION IN THE INTENSIVE CARE UNITS

Aknowledgement

First and foremost, thanks are due to GOD, the most ever kind and merciful.

To the soul of my father, I would like to dedicate this piece of work. I am sure he is sharing me my feelings right now.

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List of abbreviations:

ACCP	**American college for chest physicians**
ADP	**Adenosine diphosphate**
Ala	**alanine**
APC	**Activated protein c**
APTT	**Activated partial thromboplastin time**
AT	**Anti thrombin**
ATIII	**Anti thrombin iii**
Ca^{2+}	**Calcium ion**
CHD	**Congenital heart disease**
CNS	**Central nervous system**
COPD	**Chronic obstructive pulmonary disease**
CRCL	**Creatinine clearance**
CVL	**Central venous line**
DA	**Dalton**
DAG	**Di acyl glycerol**
DNA	**Deoxy ribo nucleic acid**
DTI	**Direct thrombin inhibitors**
DUS	**Duplex ultrasonography**
DVT	**Deep venous thrombosis**
FFP	**Fresh frozen plasma**
GCS	**Graded compression stockings**
GI	**Gastro intestinal**
GLA	**Glutamate residue**
GPIb	**Glycoprotein I b**
GPIIb	**Glycoprotein II b**
GPIIIa	**Glycoprotein III a**
HIT	**Heparin induced thrombocytopenia**
HMWK	**High molecular weight kininogen**
ICH	**Intra cranial hemorrhage**
ICU	**Intensive care unit**
INR	**International normalized ratio**
IP_3	**Inositol triphosphate**
IPC	**Intermittent pneumatic compression**
ISI	**International sensitivity index**
IV	**Intra venous**
LDUH	**Low dose unfractionated heparin**
LMWH	**Low molecular weight heparin**
Lys	**lysine**

MLCK	**Myosin light chain kinase**
$NAPC_2$	**Nematode anticoagulant peptide C_2**
PAI	**Plasminogen activator inhibitor**
PC	**Protein c**
PE	**Pulmonary embolism**
PICU	**Pediatric intensive care unit**
PIP_2	**Phosphatidyl inositol diphosphate**
PK	**Prekallikrein**
PKC	**Protein kinase C**
PLC	**Phospholipase C**
PT	**Prothrombin time**
RBC	**Red blood corpuscle**
SNAC	**Sodium N-amino caprylate**
SPCA	**Serum prothrombin conversion accelerator**
sc	**subcutaneous**
STM	**Soluble thrombomodulin**
TED	**Thromboembolism deterrant**
TF	**Tissue factor**
TFPI	**Tissue factor pathway inhibitor**
TPA	**Tissue plasminogen activator**
TPN	**Total parenteral nutrition**
TXA_2	**Thromboxane A_2**
UFH	**Unfractionated heparin**
UVC	**Umbilical vein catheter**
VKA	**Vitamin k antagonist**
VTE	**Venous thromboembolism**
vWF	**Von willebrand factor**

INTRODUCTION

Rationale for thromboprophylaxis

Most hospitalized patients have one or more risk factors for venous thromboembolism (VTE). These risk factors are generally cumulative. For example, patients with fractures of the hip are at particularly high risk for VTE because of their usual advanced age, the presence of a proximal lower extremity injury as well as its operative repair, and the frequent marked reduction in mobility for weeks after surgery. If cancer is also present, the risk is even greater. Without prophylaxis, the incidence of objectively confirmed, hospital-acquired deep venous thrombosis (DVT) is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery One quarter to one third of these thrombi involve the proximal deep veins, and these thrombi are much more likely to produce symptoms and to result in pulmonary embolism (PE).[1,2,3]

In many of these patient groups, VTE is the most common serious complication. Approximately 10% of hospital deaths are attributed to PE. For example, among 1,234 hospitalized patients who died and underwent autopsy within 30 days of a surgical procedure, the rate of PE was 32%, and PE was considered to be the cause of death in 29% of these cases. In a second study of 51,645 hospitalized patients, the prevalence of acute PE was 1%, and PE was believed to have caused or contributed to death in 37% of these cases. Although improved patient care may have attenuated some of the risk factors for VTE, patients currently in the hospital may well be at greater risk than those studied in the past because of their more advanced age, greater prevalence of cancer and intensive cancer therapy, more extensive surgical procedures, and prolonged stays in a critical care unit.[4]

Most studies of VTE and its prevention have used sensitive diagnostic tests to detect DVT. The majority of the thrombi diagnosed by these screening tests were confined to the calf, were clinically silent, and remained so without any adverse consequences. However, approximately 10 to 20% of calf thrombi do extend to the proximal veins, and, particularly in patients undergoing major surgery involving the hip, isolated femoral vein DVT is common. There is also a strong association between asymptomatic DVT and

the subsequent development of symptomatic VTE.[For example, one study found that among critical care patients with asymptomatic DVT detected by screening duplex ultrasonography (DUS) there was a significantly greater rate of PE development during their index hospitalization compared to those patients without silent DVT (11.5% vs 0%, respectively; p = 0.01). Furthermore, the in-hospital case-fatality rate of VTE is 12%, and the data suggest a case-fatality rate at 1 year of 29 to 34%.[5,6,7]

While high-risk groups for VTE can be identified, it is not possible to predict which individual patients in a given risk group will develop a clinically important thromboembolic event. Furthermore, massive PE usually occurs without warning, and there is often no potential to resuscitate patients who experience this complication. In 70 to 80% of patients who die in the hospital of PE, this diagnosis was not even considered prior to death. Although the prevention of fatal PE remains the top priority for prophylaxis programs, this outcome is uncommon in most hospital groups. Furthermore, the prevention of fatal PE is not the only objective of thromboprophylaxis. The prevention of symptomatic DVT and PE are also important objectives since these outcomes are associated with considerable acute morbidity, substantial consumption of resources, and long-term sequelae of clinical and economic significance.[8,9]

The majority of symptomatic VTE associated with hospital admissions occur after hospital discharge. When symptomatic hospital-acquired VTE is suspected, costly diagnostic testing procedures are required and, if VTE is confirmed, therapeutic anticoagulation therapy, with its potential for serious bleeding complications, should be instituted. Therefore, the failure to prevent VTE also results **in** delayed hospital discharge or readmission, **in** complications from anticoagulation therapy, **in** an increased risk of long-term morbidity from the post-thrombotic syndrome, and **in** recurrent thrombosis **in** the future. A high proportion of venous thrombi leave residual venous abnormalities including persistent occlusion and/or venous valvular incompetence. Post-thrombotic syndrome may result **in** chronic leg swelling, discomfort, dermatitis, and leg ulcers, reduces patient quality of life, and has considerable adverse economic effects. These delayed consequences of inadequate prophylaxis are often overlooked.[10,11,12,13]

Reliance on symptoms or signs of early DVT is an unreliable strategy to prevent clinically important thromboembolic events. The first manifestation of VTE may be fatal PE. The routine screening of patients for

asymptomatic DVT is logistically difficult and is neither effective in preventing clinically important VTE nor cost-effective. Accordingly, prophylaxis against VTE remains the most appropriate strategy to reduce the sequelae of venous thromboembolism.[14]

A vast number of randomized clinical trials over the past 30 years provide irrefutable evidence that primary thromboprophylaxis reduces DVT, PE, and fatal PE.[PE is the most common preventable cause of hospital death and is the number one strategy to improve patient safety in hospitalsThe Agency for Healthcare Research and Quality has published a report entitled "Making Health Care Safer: a Critical Analysis of Patient Safety Practices.This systematic review ranked 79 patient safety interventions based on the strength of the evidence supporting more widespread implementation of these procedures. The highest ranked safety practice was the "appropriate use of prophylaxis to prevent VTE in patients at risk." This recommendation was based on overwhelming evidence that thromboprophylaxis reduces adverse patient outcomes while, at the same time, decreasing overall costs.[15,16]

Concerns are sometimes raised about the complications of thromboprophylaxis, especially bleeding. However, abundant data from metaanalyses and placebo-controlled, blinded, randomized clinical trials have demonstrated little or no increase in the rates of clinically important bleeding with prophylactic doses of low-dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or a vitamin K antagonist (VKA). There is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective. Thromboprophylaxis, therefore, provides an opportunity both to improve patient outcomes and also to reduce hospital costs.[17,18]

RISK FACTOR ASSESSMENT AND STRATIFICATION

Three main factors precipitate venous thrombosis:

١. Stasis of blood;
٢. Damage to vascular structures; and
٣. Disordered hemostasis (transient or chronic hypercoagulability).

These factors have been referred to as "Virchow's triad," named for the nineteenth century pathologist, Rudolf Virchow, who showed that pulmonary thrombi generally originated in the deep veins of the systemic circulation and were carried to the pulmonary circulation by venous blood flow (although he was not who originally described the triad that bears his name).Without prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery (table 1) [19,20]

TABLE 1 : ***Absolute Risk of DVT In Hospitalized Patients***

Patient Group	**DVT Prevalence, %**
Medical patients	10 –20
General surgery	15 –40
Major gynecologic surgery	15 –40
Major urologic surgery	15 –40
Neurosurgery	15 –40
Stroke	20 –50
Hip or knee arthroplasty, hip fracture surgery	40 –60
Major trauma	40 –80
Spinal cord injury	60 –80
Critical care patients	10 –80

Geerts et al; chest 2001

Common and important causes of stasis, vascular damage, and altered coagulability are shown below. In general, the more risk factors present, the higher the risk of VTE, and elderly patients are far more likely than younger patients to have multiple risk factors.[21,22]

Conditions predisposing to venous thromboembolism:

STASIS OF BLOOD

Impaired mobility or ambulation (hospitalization or institutionalization)
Anesthesia
Valvular incompetence of leg veins (varicose veins)
Congestive heart failure
Prolonged bed ridden

DAMAGE TO VESSELS

Surgery specially pelvic procedures
Falls or fractures
Vascular catheters
Prior VTE with or without residual thrombus
Atherosclerosis

ALTERED COAGULATION

Malignancy
Inflammation (infections, rheumatic disease, tissue trauma)
Medications (hormone replacement, estrogen receptor modulators, chemotherapy)
Smoking
Hereditary or acquired thrombophilia
Nephrotic syndrome
Obesity
Pegnancy

Risk factor stratification

There are two general approaches to making thromboprophylaxis decisions. One approach considers the risk of VTE **in** each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Prophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assessment models for DVT have been proposed to assist with this process. Because the approach of individual prophylaxis prescribing, based on formal risk-assessment models, has not been adequately validated and is cumbersome without the use of computer technology, it is unlikely to be used routinely by most clinicians. Furthermore, there is little formal understanding of how the various risk factors interact to determine the position of each patient along a continuous spectrum of thromboembolic risk.[21,22,23,24]

One simplification of this process for surgical patients involves assigning them to one of three VTE risk levels based on

- the type of operation (*eg*, minor or major),
- age (*eg*, < 40 years, 40 to 60 years, and > 60 years), and
- the presence of additional risk factors (*eg*, cancer,obesity or previous VTE) (table 2)

Despite its limitations, this classification system, which was derived using prospective study data, provides both an estimate of VTE risk and related prophylaxis recommendations.[25,26,27,28,29]

TABLE 2: ***Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis***

Level of Risk	DVT, %		PE, %		Successful Prevention Strategies
	Calf	Proximal	Clinical	Fatal	
Low risk	2	0.4	0.2	< 0.01	No specific prophylaxis; early and "aggressive" mobilization
Minor surgery in patients < 40 yr with no additional risk factors					
Moderate risk	10 –20	2 –4	1 –2	0.1 –0.4	LDUH (q12h), LMWH (≤ 3,400 U daily), GCS, or IPC
Minor surgery in patients with additional risk factors					
Surgery in patients aged 40–60 yr with no additional risk factors					
High risk	20 –40	4 –8	2 –4	0.4 –1.0	LDUH (q8h), LMWH (> 3,400 U daily), or IPC
Surgery in patients > 60 yr, or age 40–60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)					
Highest risk	40 –80	10 –20	4 –10	0.2 –5	LMWH (> 3,400 U daily), fondaparinux, oral VKAs (INR, 2–3), or IPC/GCS + LDUH/LMWH
Surgery in patients with multiple risk factors (age > 40 yr, cancer, prior VTE) Hip or knee arthroplasty, hip fracture surgery Major trauma; SCI					

Geerts et al chest 2001