INTRODUCTION

The complications of acute deep venous thrombosis, pulmonary embolism and post-thrombotic syndrome are the most common cause of hospital death. Approximately 3000,000 die per year in United States from pulmonary embolism, the majority of which results from deep venous thrombosis ***(Silva, 1991)***.

Understanding underlying epidemiology, pathophysiology and natural history in deep venous thrombosis is essential in guiding appropriate prophylaxis, diagnosis and treatment. Deep venous thrombosis is usually silent in nature in most of hospitalized patients and usually presented by non-specific symptoms and signs ***(Haeger, 1969)***.

Components of triad described by Rudolf Virchew which includes abnormalities of thrombosis, abnormalities of blood flow and vascular injury remains applicable today ***(Sue et al., 1995)***.

There are many recognized risk factors for venous thrombo-embolism which include immobilization, surgery, malignancy, trauma, pregnancy history of previous attacks of venous thrombo-embolism be oral contraceptive drugs ***(Cogo et al., 1994)***.

Malignancy is considered one of the most important risk factors of the deep venous thrombosis and this is what we are going to focus in this research. Patietns with cancer are at increased risk of venous thrombo-embolism. Approximately

15% of malignancies are complicated by venous thrombo-enbolims with higher prevalence in autoplay studies ***(Maxwell and Bennett, 2012)***.

Thrombogenic mechanisms associated with cancer may be heterogenous, but likely they involve substances that are directly or indirectly activate coagulation. About 90% of patients with cancer have abnormal coagulation parameters including increased coagulation factors, fibrinogen and thrombocytosis. Levels of coagulation inhibitors, antithrombin, protein C & S may be reduced in malignancy ***(Falanga et al., 1994)***.

The role of cancer treatment related factors including chemotherapy has been a focus of recent investigations because most cases of venous thrombo-embolism in the oncology settings occur in ambulatory patients ***(Kirwan et al., 2003)***.

Deep venous thrombosis may have a lot of complications which gives impact on short-term life especially in patients with cancer like pulmonary embolism and postthrombotic syndrome. Thus, we have aiming to prevention, early diagnosis and treatment of deep venous thrombosis ***(Amit, 2007)***.

AIM OF THE WORK

The aim of this study is to focus on malignancy as a cause of deep venous thrombosis and related complications which has impact on short-term life.

Aiming to prophylaxis, early diagnosis and treatment of deep venous thrombosis in patients with cancer.

EPIDEMIOLOGY AND RISK FACTORS OF DEEP VENOUS THROMBOSIS

Epidemiology:

Precise definition of the incidence of acute DVT is complicated by the clinically silent nature of most thromboses in hospitalized patients as well as the non-specific signs and symptoms. The incidence depends on the population studied, the intensity of screening, and the accuracy of the diagnostic tests employed-autopsy studies, which are based by inclusion of the very sick and old have reported the prevalence of DVT to be 35% to 52% ***(Meissner and Strandness, 2005)***.

Most clinical trials and studies on the incidence of acute DVT have focused on specific inpatient groups such as postoperative patients. Although useful in defining risk factors for acute DVT, such studies provide few data regarding the overall prevalence of acute DVT. Community-based studies may provide a better estimate of overall prevalence but frequently suffer from a lack of objective documentation of DVT. Extrapolating data from a longitudinal community-based study, ***Conn et al. (1993)*** calculated an incidence of 250,000 cases of acute DVT per year in the United States. These results, however, were based largely on questionnaires and clinical findings suggestive of previous DVT.

Community-based studies of 4 venographically documented symptomatic DVT have reported a yearly incidence of 1,6 per 1000 residents ***(Nordstrom et al., 1992)***.

Among men, the cumulative probability of suffering a thromboemoblic event is estimated to be 10.7% by the age of 80 years ***(Hassan and Wellin, 1997)***.

This study focuses on correlation between deep venous thrombosis and malignancy. A recognized malignancy is present in 19% to 30% of patients with DVT ***(Piccioli et al., 1996)***. Approximately 15% at malignancies are complicated by venous thromboembolism, with substantially higher prevalence in autopy studies. An association between mucin secreting gastrointestinal tumours and thrombosis has long been recognized ***(Falanga et al., 1994)***. Next table shows rates of deep venous thrombosis and pulmonary embolism in different malignancies.

Table (1): Rates of DVT/PE in different malignancies.

Site	Rate of DVT/PE per 10000 patients
Head/neck	16
Bladder	22
Breast	22
Oesophagus	43
Uterus	44
Cervix	49
Prostate	55
Lung	61
Rectal	62
Liver	69
Colon	76
Leukaemia	81
Renal	84
Stomach	85
Lymphoma	96
Pancreas	110
Brain	117
Ovary	120

An analysis of > 1.2 million US medicine (age≥ 65) patients admitted to the hospital with a malignancy ***(Levitan et al., 1999)***

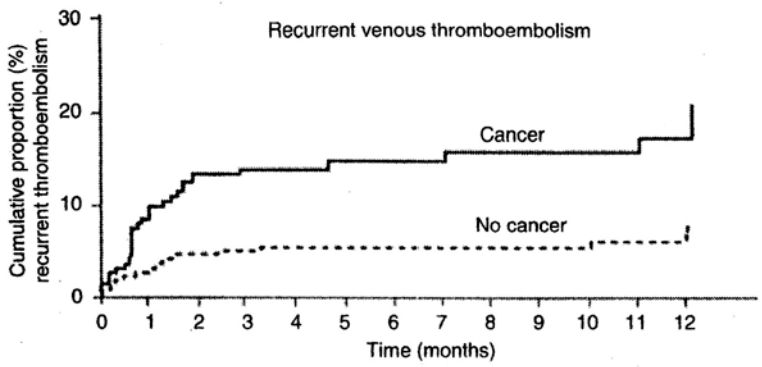

Fig. (1): Increased VTE prevalence over time in patients with cancer, but not in those without cancer ***(Stein et al., 2006)***.

Deep venous thrombosis may also herald a previously undetected malignancy in 3 to 23% of patients with idiopathic thrombosis in another 5 to 11% of patients appears within 1 to 2 years of presentation of deep venous thrombosis, malignancy. Recurrent idiopathic deep versus thrombosis is associated with a 9.8-fold higher risk than that for 2nd thrombosis, a subsequent malignancy being identified in 17.1% of patients with this disorder ***(Prandoni et al., 2002)***.

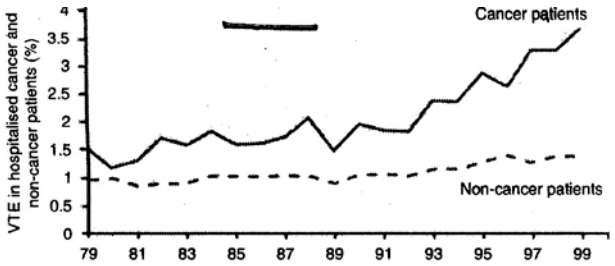

Fig. (2): Cumulative incidence of recurrent VTE during anticoagulant therapy among patients with and without cancer ***(Prandoni et al., 2002).***

Risk Factor of Acute Deep Venous Thrombosis:

The day-to-day risk of venous thromboembolism is much higher in some patients than in others. Patients at special risk are said to have a hypercoagulable state, which may be temporary or permanent. Many such patients can be identified through knowledge of recent and remote prior medical history. Venous thrombosis is more common in such high-risk patients after venous injury, including injury associated with fairly minor medical and surgical interventions ***(Ogston, 1987)***.

Intrinsic coagulaopathy:

Primary hematologic thrombogenic and hypercoagulable states may be produced by disorders of platelet number or function, defects of intrinsic or extrinsic coagulation, low levels of circulating anticoagulants, resistance to anticoagulant factors, excessive inhibitors of thrombolysis, or insufficient thrombolytic activation. They may be congenital or acquired ***(Haake and Berkman, 1986)***.

A primary deficiency of protein C or protein S leads to a hypercoagulable state in which patients often have episodes of deep venous thrombosis or pulmonary thromboembolism before 35 years of age. These patients are also at risk for premature arteriosclerotic syndromes and myocardial infarction at an early age. Acquired deficiency of these proteins can result from cancer, chemotherapy, vitamin K deficiency, oral anticoagulants, surgery and disseminated intravascular coagulation. In familial antithrombin III deficiency the circulating level may be reduced to one half the normal

amounts, with a correspondingly high risk for venous thrombosis. More than one half of affected persons have pulmonary thrombembolism before 50 years of age. Patients with severe liver disease may develop venous thrombosis from an acquired antithrombin III deficiency ***(Coller et al., 1997)***.

Deficiencies of protein C, protein S or antithrombin III each account for approximately 5% of the cases of DVT. Antiphospholipid syndrome occurs in 1-5% of population and increases with the age such that 50% of patients aged 80 years and over have antiphospholipid antibodies. The syndrome occurs in patients with lupus anticoagulants and anticardiolipin antibodies. The antibodies are directed against protein-phospholipid complexes and inhibit antithrombotic effect of endothelial cells and increase platelet activation. Those patients have a high incidence of venous and arterial thrombotic events ***(Ridker et al., 1995)***.

Impaired fibrinolysis:

Impaired fibrinolytic activity results in increased thrombus propagation and an increased likelihood of clinical venous thrombosis. Many different problems can lead to impaired fibrinolysis and a clinical risk of venous thrombosis. Plasminogen levels may be low, or plasminogen itself may be defective because of structural abnormalities. Fibrinogen and fibrin may be structurally, abnormal in such a way as to resist degradation by plasmin. A patient may have high levels of circulating inhibitors of fibrinolysis or low levels of plasminogen activators ***(Burnand, 2008)***.

Reduced fibrinolytic activity has been documented in postoperative patients, in women taking oral contraceptive medications and during pregnancy and the puerperium ***(Burnand, 2008)***.

History of DVT:

A history of venous thrombosis or thrombembolism is associated with an extremely high likelihood of recurrent venous thrombosis. Kakkar prospectively studied surgical patients and shows that a history of DVT raises the likelihood of new postoperative venous thrombosis from 26% to 63%, and a history of both DVT and PE, raises the likelihood of new postoperative venous thrombosis to 100% ***(Simioni et al., 1997)***.

In general, persons with a history of venous thrombosis are five times more likely to have a new DVT than those who have not had prior episodes. This is partly because the group of patients who have had prior DVT includes many patients with other irreversible risk factors and partly because prior DVT leaves permanent venous abnormalities such as endothelial irregularity, chronic venous stasis and valvular damage all conditions that predispose to a recurrence ***(Simioni et al., 1997)***.

Surgery

Surgery constitutes aspectrum of risk that is influenced by patient age thrombotic risk factors, type of procedure, extent of surgical trauma, length of procedure and duration of postoperative immobilization. All components of Virchow's traid may be present in surgical patient-immobilization,

transient changes in coagulation and fibrinolysis and the potential for gross venous injury ***(Clagett et al., 1995)***.

Postoperative DVT may occur in response to even minimal venous endothelial injury. Most cases of postoperative DVT are believed to start in the area of the valve cusps, where stasis is at a maximum. Metanalysis of 7,500 patients from prospective clinical trials comparing prophylactic subcutaneous heparin with no prophylaxis for surgical procedures reveals an unexpectedly high incidence of thrombosis and embolism for patients who did not receive prophylaxis. The average incidence of DVT in the group without prophylaxis ranges from a high of 48% after orthopedic surgery for traumatic injuries to a low of 12% after elective general surgery. In this meta-study, approximately 20% of the patients with DVT developed PE one third of these patients died. Other authors report that PE occurs in 5% to 10% of patients undergoing elective orthopedic surgery and that 46% of all deaths in this orthopedic population are due to PE. Non-elective surgery for his fractures has been reported to carry a 70% risk of DVT ***(Heit et al., 1999)***.

Heit et al. (1999) found a nearly 22-fold higher risk of deep venous thrombosis and pulmonary embolism among patients who were hospitalized following previous surgery.

Catheter-associated thrombosis:

Five early clinical series find that up to 33% of patients develop catheter-associated thrombus after femoral vein

cannulation. The incidence of femoral vein thrombosis increases to 50% when 25% dextrose solutions are infused through a femoral vein catheter. A recent clinical survey suggests that the incidence of this problem remains high today ***(Mian et al., 1994)***.

The risk does not depend on prolonged femoral vein catheterization. DVT resulting in major PE has been reported in a young woman on oral contraceptives who underwent only 30 minutes of femoral vein catheterization ***(Mian et al., 1994)***.

Subclavian and axillary vein thrombosis once were rare and reportable entities, but increases in the prevalence of IV drug abuse, trans-venous pacemakers, and long-term central venous catheters have made catheter-associated subclavian vein thrombosis a fairly common clinical entity. Some studies demonstrate subclavian vein thrombosis in up to 40% of patients receiving chemotherapy or parenteral alimentation through subclavian catheters. Subclavian and axillary vein thrombosis is also seen in association with Swan-Ganz catheters and may produce a significant morbidity ***(Becker et al., 1996)***.

Anesthesia:

General anesthesia is an independent risk factor for the development of DVT after surgery. For example, patients randomized to receive general anesthesia for retropubic prostatectomy had a 52% incidence of postoperative DVT, whereas those randomized to epidural anesthesia had a DVT incidence of only 12% ***(Poikolainen and Hendolin, 1994)***.

Immobility:

Immobility is one of the most important risk factors for venous thromboembolism. In a prospective study suing radiolabeled fibrinogen scanning, Cade finds acute thrombosis of the deep veins in 10% of patients placed at bed rest in a general medical ward, and in nearly 30% of the much sicker patients placed in an intensive care unit.

The incidence of venous thromboembolism at autopsy is 15% in patients dying from any cause after less than 1 week at bed rest, but rises to 80% in patients who die after more prolonged immobilization. The singular importance of immobilization is evidenced by a study of hemiparetic stroke patients: fibrinogen scanning detected DVT in 60% of paralyzed legs but in only 7% of non-paralyzed ones ***(Bauer, 1993)***.

Autoimmune disease and immune deficiency:

Spontaneous deep venous thrombosis occurs in at least 9% of patients with systemic lupus erythematosus (SLE), and the recurrence rate in this population is high. The "lupus anticoagulant" that is believed to be responsible for this excess risk is also seen in acquired immunodeficiency syndrome (AIDS) and in many autoimmune diseases besides lupus. In patients without autoimmune disease, the lupus anticoagulant may be induced by drugs, most notably the phenothiazines. The lupus anticoagulant is one of the more important risk factors that can be identified by testing ***(Khamashta et al., 1995)***.

Cancer:

Malignancy, whether known or occult, is a recognized risk factor for venous thromboembilism. The thrombogenic mechanism associated with cancer may be heterogeneous, but likely they involve release of substances that directly or indirectly activate coagulation. Tissue factor and cancer procoagulant, a cystiene protease activator of factor X, are the primary tumor cell procoagulants; associated macrophages may also produce procoagulants as well as inflammatory cytokines. Elevated fibrinogen level and thrombocytosis are the most common abnormalities, in addition; levels of the coagulation inhibitors (antithrombin, protein C & S) may also be reduced in malignancy ***(Hull and Pineo, 1992)***.

Chemotherapy:

Chemotherapy increases the risk of DVT and PE above and byond the risk associated with, the underlying cancer. Some chemotherapeutic agents act to decrease circulating anticoagulants such as antithrombin III, protein C, or protein S. Other causes an increase in circulating procoagulants such as Von Willebrand factor. There is some evidence for a chemotherapeutic depression of normal fibrinolytic activity ***(Messner and Strandness, 2005)***.

Inflammatory bowel disease:

Ulcerative colitis and Crohn's disease are associated with an excess risk of DVT and PE caused by elevations of fibrinogen, factor VIII, and platelet activity, and by depressions of antithrombin III and alpha2-macroglobulin levels ***(Lambrecht et al., 1997)***.

Cerebrovascular accidents and neurotrauma:

The incidence of DVT is extremely high after stroke or neurological trauma. In one study, fully one half of patients developed acute DVT within a median time of 5 days after a stroke ***(Mellbring et al., 1996)***.

Head trauma results in syndromes of defibrination, disseminated intravascular coagulation, and venous thromboembolism, and DVT is a complication in up to 40% of postoperative neurosurgical patients ***(Saizman, 1993)***.

Pregnancy and puerperium:

Deep and superficial thrombophlebitis and PE are of great concern in pregnancy and in the postpartum period. PE is the most common non-traumatic cause of maternal death during pregnancy. At one time it was thought that the risk was even higher in the postpartum period, but this now seems doubtful. Rutherford finds that 75% of the cases of clinically apparent DVT in 169,776 pregnant women occurred before delivery and one half are in the first 15 weeks of pregnancy ***(Paiement, 1994)***.

Exogenous estrogens:

Oral contraceptive use raises the risk of DVT and PE but the magnitude of the risk is difficult to quantify. There have been no prospective randomized studies using definitive testing to compare the incidence of DVT or PE in patients with and without oral contraceptives. Case-control and cohort studies based on clinical signs and symptoms of thrombosis suggest a relative risk somewhere between 3 and 12 times higher for patients taking oral contraceptives compared with those not taking them ***(Helmirch et al., 1997)***.

Polycythemia and thrombocytosis:

In general, the risk of thrombosis increases linearly with increasing hematocrit. A retrospective review determines that 40% of deaths in patients with polycythemia vera are related to arterial or venous thrombosis. It would seem logical that thrombocytosis should also raise the risk of thrombosis, but in fact there are no good data to support this belief. In fact, several studies show that a platelet count above one million leads to a reduced likelihood thrombosis and an increased likelihood of bleeding problems ***(Buss et al., 1995)***.

Blood group:

There is some evidence that type A blood is associated with lower levels of antithrombin III and higher levels of factor VIII than type 0 blood. Women of reproductive age with type A blood have venous thrombosis two to four times more often than women with type 0 blood. This increased risk seems to extent to pregnant women and, those on oral contraceptive