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Evaluation of Prophylaxis and Management of Venous Thromboembolism in Surgical Cancer Patients

Omar Mokhtar Elhayeg, Abdelaziz Ahmed Abdelhafez, Mohamed Alaa Eldin Beshta
Department of Vascular Surgery, Faculty of Medicine - Alazhar University
Corresponding author: Mohamed A.E. Beshta, Mobile: 01063232395; Email: mohamedalaa26111988@gmail.com

ABSTRACT

Background: Deep venous thrombosis is considered to be one other challenges in medical practice because of silent nature in most of the cases and the complications that may end with death. It's very difficult to study its incidence. There is strong relation between malignancy and thrombosis. The incidence of deep venous thrombosis in malignancy differs according to the type of the tumor. There are many risk factors of deep venous thrombosis other than malignancy like surgery, history of previous attack, immobility, obesity, pregnancy, and contraceptives, and others. The incidence differs from one risk factor to another and also according to presence of other co-morbidities. Venous thrombosis occurs as a result of one or more three factors postulated by Virchow either abnormalities of blood flow, abnormalities of blood or vascular injury. Deep venous thrombosis in malignancy may be due to other causes like surgery, chemotherapy or central venous catheters.

Objective: The aim of this work was to evaluate the efficacy of prophylactic measures before, during and after surgery in reducing the risk of developing venous thromboembolism in cancer patients undergoing surgery and how to mange the thromboembolic events if occurred after surgery in surgical cancer patients.

Patients and Methods: This is a prospective study conducted on 20 patients presented to the Oncology surgery unit and Vascular surgery outpatient clinic of AL-Hussein University Hospital and Ahmed Maher Teaching Hospital between December, 2017 and June, 2018. Patients with operable tumors were included in this study while cancer patients with comorbidities interfering with surgical procedures were excluded. Data were recorded in predesigned sheet including age, sex, special habits, obesity, history of previous DVT and history of chronic illness. Duplex study was done pre and post operative to diagnose DVT .Time of operations were assessed. All included patients were assessed for the appropriate regimen of prophylaxis either mechanical or pharmacological or combination of both. Diagnosed patients with DVT after surgery were treated with heparin and oral anticoagulants. **Results:** Of the 20 patients, 9 (45%) were females and 11(55%) were males. The age of the patients ranged between 33 and 82 years with a mean age at presentation was 59.85 years.

With the 20 patients who used preoperative prophylaxis regimens, the incidence of postoperative deep vein thrombosis was 10%; with average time of DVT development of (1.25 ± 0.35) months. In addition, the rate of bleeding was 5%; developed at 1-month duration.

Conclusion: patients with cancer particularly those undergoing surgery are at risk of developing venous thromboembolic complications. Low molecular weight heparin (LMWH) and Unfractionated heparin (UFH) prophylaxis in patients undergoing cancer related surgery has proved to be effective and safe in reducing the risk of an acute event. Thromboprophylaxis with LMWH, UFH and mechanical methods should be considered for all patients with a malignancy who undergo surgery.

Recommendation: Both pharmacological and mechanical thromoboprophylaxis measures are required to minimize the risk of developing deep vein thrombosis and its complications in surgical cancer patients (SCP).

Keywords: Venous thromboembolism - deep vein thrombosis - Low-molecular-weight heparin - unfractionated heparin.

INTRODUCTION

The association between cancer and thrombosis has been known since at least the 19th century. Cancer-associated venous thromboembolism (VTE) has significant clinical consequences for patients. Thromboembolism is a leading cause of death in cancer patients and cancer patients who develop VTE have a significantly worse survival [(1)].

Venous manifestations of cancer-associated thrombosis include deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as visceral or splanchnic vein thrombosis, together described as VTE [(2)]. Cancer continues to pose a costly and growing international threat toward modern day society.

Among its many direct and indirect complications is its role as a major risk factor for venous thromboembolism (VTE), discovered in a fifth of all cancer patients and as many as half on postmortem examination [(3)]. It is well established that cancer patients are at an increased risk of venous thromboembolism (VTE). In fact, the presence of malignancy increases the risk of (VTE) by a factor of 4 to 6, and large population-based studies showed that the incidence of VTE is on the rise [(4)].

Understanding underlying 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 [(5)].

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In1856 a German pathologist Rudolf Virchow postulated the interplay of three processes resulting in venous thrombosis known as Virchow triads. These triads are description for the components of the risk factors of deep venous thrombosis which include abnormalities of: thrombosis, abnormalities of blood flow and vascular injury remain applicable today [(6)].

Historically, in 1823, the French physician Jean-Baptiste Bouillaud published what appears to be the first report of an association between cancer and thrombosis. In 1865, another French physician Armand Trousseau reported an association between gastric cancer and venous thrombosis almost 150 years ago, yet its exact pathophysiology remains poorly understood. These reports considered the beginning of attention that malignant disease and hemostasis interact together [(7)].

Overall, cancer patients constitute 20%-30% of the patients diagnosed with VTE, and depending on the type of tumor, extent of malignancy, type of cancer treatment, and presence of other risk factors, 1%–25% of patients with malignancy will develop thrombosis [(8)].

Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions, and immobilization; the presence of an indwelling central catheter; chemotherapy; and new molecular targeted therapies. Furthermore, other comorbid features will also influence the overall of thrombotic complications, as they do in patients without cancer [(9)].

About 90% of patients with cancer have abnormal coagulation parameters including increased coagulation factors, fibrinogen and thrombocytosis. Thrombogenic mechanisms associated with cancer may be heterogeneous, but likely they involve substances that are directly or indirectly activate coagulation. Levels of coagulation inhibitors, protein C & S and antithrombin may be reduced in malignancy [(10)].

Diagnosis of DVT is very challenging as the limb that entirely normal clinically may be has a life threatening thrombus and the limb with typical symptoms and signs of DVT may prove to be normal. Diagnosis is by clinical assessment, imaging and by biological testes [(11)].

A number of guidelines for the prevention and management of VTE in cancer patients have been released from major American and European scientific societies. Effective prophylaxis and treatment of VTE reduced mortality and morbidity, and improved quality of life. Low-molecular-weight heparin (LMWH) is preferred as an effective and safe means for prophylaxis and treatment of VTE. It has largely replaced unfractionated heparin (UFH) and vitamin K antagonists (VKAs) [(7)].

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 post thrombotic syndrome. Thus, we aimed at preventing, early diagnosis and treatment of deep venous thrombosis [(12)].

AIM OF THE WORK

The aim of this study was to evaluate the efficacy of pharmacological and mechanical thromboprophylactic measures in reducing the risk of developing of VTE in cancer patients undergoing surgical procedures and management methods of venous thromboembolic events if occurred after surgery in surgical cancer patients.

PATIENTS AND METHODS

This study was conducted on 20 patients who had operable tumors, attending at Oncology surgery unit and Vascular surgery outpatient clinic of AL-Hussain University Hospital and Ahmed Maher Teaching Hospital .Approval of the ethical committee and a written informed consent from all subjects were obtained. This study was conducted between December 2017 and June 2018.

Inclusion criteria: Diagnosed operable cancer patients.

Exclusion criteria: Cancer patients with major comorbidities interfering with anesthesia and surgical procedures e.g. cardiac, respiratory, renal and hepatic. To avoid bleeding complications these groups were excluded: Absolute contraindication: 1. Active internal bleeding. 2. Recent eye operations. 3. Recent central nervous system surgery. Relative contraindications: I- Relative major contraindications: 1. Recent serious gastrointestinal bleeding. 2. Recent serious trauma. 3. Severe hypertension (> 200 mmHg systolic blood pressure or >110 mmHg diastolic blood pressure). II- Relative minor contraindications: 1.Recent minor trauma, including cardiopulmonary resuscitation. 2. Haemostatic defects including those associated with severe hepatic or renal disease. 3. Pregnancy and puerperium.

Mechanical and pharmacological prophylaxis measures were applied for all included patients before, during and after surgery .Mechanical measures included graduated compression stockings or intermittent pneumatic compression devices before surgery, Electrical muscle stimulation during operation and early ambulation after surgery .Pharmacological regimens used were either low molecular weight heparin(LMWH) with a dose of 40 IU subcutaneous (SQ) injection 12 hours before operations and 40 IU SQ injection once per day for one week after surgery or unfractionated heparin(UFH) with a dose of 5000 Units SQ injection given 6 hours before operations and 5000Units SQ injection two or three times daily for one week after operations. Time of pharmacological prophylaxis regimens were extended up to 4 weeks after major pelvic or abdominal operations.

Operations were classified according to time of operations into major operations lasting more than

45minutes and minor operations lasting less than 45 minutes. Post operatively, all patients were assessed regularly clinically and duplex study was done to detect any VTE events.

Patients developed DVT after surgery were treated with heparin for 10-14 days and oral anticoagulant with warfarin was started within 24 hours of initiating heparin to maintain a target international normalization ratio (INR) of 2-3 for at least 6 months.

RESULTS

Statistical analysis was carried out using MedCalc ver. 15.8. (MedCalc, Ostend, Belgium). Quantitative data were expressed as mean and Standard deviation (± SD) .Qualitative data were expressed as frequency and percentage. Tests of significance (Student's t, Chi square, McNemar's, logistic regression analysis and Pearson's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant.

Table (1): Socio-demographic data among 20 CSP:

Variables		Range	Frequency (%)
Age (years)		33 – 82	59.85 ± 14.18*
Gender	Female		9 (45%)
	Male		11 (55%)

This table shows that; the mean age of all patients was (59.85 ± 14.18) years. Regarding gender of the patients, (55%) of patients were males; while (45%) were females.

Table (2): Comorbidities among 20 CSP patients:

Variables	Frequency (%)
Smoking	8 (40%)
DM	9 (45%)
Obesity	8 (40%)
IHD	5 (25%)
CVS	1 (5%)
Previous DVT	8 (40%)

This table displays that; (40%) of patients were smokers, (45%) of patients had DM, (40%) of patients had obesity, (25%) of patients had IHD, (40%) of patients had history of previous DVT, and only (5%) had CVS.

Table (3): Pre-operative Duplex data among 20 CSP patients:

Variables		Frequency (%)
Pre-operative Duplex	DVT	0 (0%)
	Normal	20 (100%)

This table indicates that; nobody had pre-operative DVT during initial Duplex assessment.

Table (4): Intra-operative data among 20 CSP patients:

Variables		Frequency (%)
Type of operation	Major operation	7 (35%)
	Minor operation	13 (65%)
Intra-operative DVT		0 (0%)
Operative time (minutes)		118.5 ± 49.1

This table demonstrates that; nobody had intra-operative DVT; with average operative duration of (43± 7.25) minutes.

Regarding type of operation, most (65%) of patients had minor cancer operations; while (35%) had major cancer operations.

Table (5): Post-operative outcomes (Duplex) data among 20 CSP patients:

Variables		Frequency (%)
DVT		2 (10%)
Time of DVT development (month)		1.25 ± 0.35
Level of DVT	Calf veins	1 (5%)
	Ilio-femoral veins	1 (5%)
Wound hematoma or bleeding		1 (5%)
Time of bleeding (month)		1*

This table reveales that; (10%) had post-operative DVT; with average time of DVT development of (1.25 ± 0.35) months.

Regarding wound hematoma or bleeding, only one patient (5%) had wound bleeding; developed at 1-month duration.

Table (6): Comparison between the 2 groups as regards to age and sex using Student's t and Chi square tests:

Variable		Coagulopathy group (3)	Normal group (17)	Student's t test
		Mean ± SD	Mean ± SD	P value
Age (years)		74.33 ± 7.09	57.29 ± 13.65	= 0.05*
Variable		Coagulopathy group (3)	Normal group (17)	Chi square test
				P value
Gender	Female	1 (33.3%)	8 (47.1%)	= 0.850
	Male	2 (66.7%)	9 (52.9%)	

Comparative study between the 2 groups revealed; significant increase in age in coagulopathy group; compared to normal group; with significant statistical difference (p = 0.05).
Comparative study between the 2 groups shows a non-significant difference as regards gender of patients (p > 0.05).

Table (7): Pearson's correlation analysis for baseline clinical/pre and intra-operative Factors associated with post-operative coagulopathy:

Associated Factor	Post-operative coagulopathy	
	R	P
Age (years)	0.462	=0.04*
FBS (mg/dL)	-0.0313	=0.895
PT (seconds)	0.509	=0.021*
aPTT (seconds)	0.152	=0.521
INR	0.491	= 0.027*
Operative time (minutes)	0.1009	=0.672

Pearson's correlation analysis shows that; age, pre-operative PT and INR had a highly significant positive correlation with post-operative coagulopathy; with highly significant statistical difference (p < 0.01 respectively).

Table (8): Logistic regression model for the Factors affecting coagulopathy occurrence using Forward method:

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	-19.2986		
Age	0.13247	0.056151	0.0183*
PT	0.54432	0.21422	0.0111*

Logistic regression analysis displays that; after applying (Forward method) and entering some predictor variables; the increase in age and pre-operative PT; had an independent effect on increasing the probability of coagulopathy occurrence; with significant statistical difference (p < 0.05 respectively).

DISCUSSION

Approximately 15% of malignancies are complicated by venous thromboembolism with higher prevalence in autopsy studies [13].
VTE is a common complication in cancer surgical patients. The presence of malignant disease double the risk for DVT, with reported incidence of asymptomatic calf vein thrombi at 40 to 80%, proximal vein thrombi 10% to 20%, pulmonary embolism 4% to 10% and fatal PE 1% to 5% without preoperative thromboprophylaxis.
This study was conducted on 20 patients presented to the oncology surgery unit and vascular surgery outpatient clinic of AL-Hussein University Hospital and Ahmed Maher Teaching Hospital between December, 2017 and June, 2018 with diagnosed operable tumors. The 20 patients included in this study 9 were females (45%) and 11 (55%) were males, with female to male ratio 1:1.22. The age of the patients ranged between 33 and 82 years with mean age of the patients 59.8.
Another study conducted by **Kroger [14] indicated** that there were 507 surgical cancer patients 53% male and 47% females with mean age 68 years. In our study, there were 8(40%) patients had a special habit of smoking while in study conducted by **Clayburgh *et al.* [15],** 74% of patients had history of smoking. In our study, there were 8 (40%) patients had a history of obesity similar to results found by **Dhakal *et al.* [16]** in which percentage of obesity of cancer patients undergoing surgery was 25%. In the present study, there were 5 (25%) patients with history of arterial embolism in the form of ischemic heart disease that is closely related to the conclusion of **Alok *et al.* [1]** where the rate of the patients with positive history of IHD were 17.4%. In our study, there were 8 patients (25%) with history of previous deep vein thrombosis that is nearly closed to the results found by **Kroger [14]** with history of DVT in 33% of the patients.
In the present study, the rate of incidence of deep vein thrombosis after surgery in the included surgical cancer patients was 10% in which 2 patients developed DVT postoperative , one of them 30 days and the other patient 45 days after surgery.One patient had calf vein thrombosis and the other had extensive ilio-femoral vein thrombosis that occurred after major abdominal operation. In cancer patients undergoing surgery without thromboprophylaxis, the rates of DVT and fatal PE ranges from 15% to 30% and from0.2% to 0.9% respectively. The clinical value of thromoprophylaxis has been confirmed by meta-analysis of randomized trials in which the prophylactic regimens was compared with no prophylaxis. The frequency of DVT was significantly reduced by thromoprophylactic measures from 22% to 9% [17].
These results resemble those published by **Agnelli [17]**.In studies conducted by **Bergqvist *et al.* [18]**,they found that the rate of venous thromboembolism at the end of the double -blind phase were 12 percent in the patients with thromboprophylactic measures, and the rate of fatal PE was 2.2% and there were no significant difference in bleeding complication at the end of the double-end study that nearly coincide with our results . In this study, it was found that the rate of incidence of D.V.T was 10% and the rate of bleeding complication was 5%. The results of this

study agree with those of a meta-analysis of pre-operative prophylaxis that had been demonstrated a reduced incidence of VTE in patients who received heparin thromboprophylaxis (13.6%) [(19)].In our study, the surgical cancer patients underwent major pelvic or abdominal operations were 7 (35%) patients, the rate of incidence of DVT among surgical cancer patients underwent major pelvic or abdominal operations was 14.3%.

Rasmussen *et al.* [(20)] showed that prolonged prophylaxis with LMWH after major abdominal and pelvic significantly reduces the risk of VTE. The overall incidence of VTE was 14.3% (95% CI, 11.2–17.8%) that is similar to the present study.

In the present study, among the included twenty surgical cancer patients only one (5%) patient developed postoperative bleeding after one month of extended pharmacological thromboprophylaxis with unfractionated heparin.

In our study, the patients who developed DVT postoperative and received warfarin as an oral anticoagulant treatment showed significant increase of prothrombin time and international normalization ratio (INR) to the level of therapeutic range (2-3).

CONCLUSION

Patients with cancer particularly those undergoing surgery are at risk of developing venous thromboembolic complications. Low molecular weight heparin (LMWH) and Unfractionated heparin (UFH) prophylaxis in patients undergoing cancer related surgery proved to be effective and safe in reducing the risk of an acute event. Thromboprophylaxis with LMWH, UFH and mechanical methods should be considered for all patients with malignancy diseases who undergo surgery.

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