

# FREQUENCY OF DEEP VENOUS THROMBOSIS IN CANCER PATIENTS IN A TERTIARY CARE HOSPITAL

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## ABSTRACT

**Objective:** To find out the frequency of deep venous thrombosis (DVT) and venous thromboembolism (VTE) in cancer patients.

**Material and Methods:** In order to find out the incidence of DVT/VTE in cancer patients a prospective study was conducted in the medical oncology unit at Hayatabad Medical Complex, Peshawar from January 2010 to June 2011.

**Results:** Out of 1200 total cancer admissions, 35 patients were found to have venous thromboembolism. Age distribution was 5-60 years. Twenty one were males and 14 females. Seventeen patients had solid organ tumours while 18 patients had haematological malignancies. These patients were treated with inj enoxaparin 1mg/kg/day for 5-7 days, followed by warfarin for 4-6 months or longer.

**Conclusion:** Every patient with malignancy should be regularly assessed for risk of DVT/VTE as part of the standard procedure for hospital attendance.

**Key Words:** neoplasm, low molecular weight heparin, warfarin, deep vein thrombosis.

## INTRODUCTION

It has been well known since the 19<sup>th</sup> century that patients with cancer have an increased risk for venous thromboembolism (VTE), compared with those without cancer<sup>1</sup>. Active cancer with and without chemotherapy increases the risk of venous thromboembolism by 5-6 fold. Overall, cancer patients constitute 15-20% of the patients diagnosed with VTE.<sup>2</sup> Furthermore cancer associated thrombosis is linked with poor prognosis. It is the second leading cause of death in cancer patients<sup>3</sup>.

In a recent cohort study, the incidence of venous thromboembolism during the first six months after cancer diagnosis was 12.4 per 1000<sup>4</sup>. The frequency of venous thromboembolism (VTE) is rising in patients with cancer and VTE contributes to mortality and morbidity<sup>5</sup>. Most common cancers in patients with VTE are lung, breast, colorectal and prostate<sup>6</sup>. The life expectancy is also shortened with concomitant diagnosis of VTE. The increase in mortality is partly attributable to fatal pulmonary embolism, but it also reflects the advanced stages of cancer and

underlying aggressive tumor biology in these patients. The risk of VTE in cancer patients varies according to disease specific factors such as the location, stage, and type of malignancy<sup>7</sup>. Cancer patients undergoing surgery have up to twice the risk of DVT and three times the risk of pulmonary embolism as non cancer patients undergoing similar operations<sup>8</sup>. VTE risk is further increased by cancer therapies<sup>9</sup>. Therefore there is a clear need for thromboprophylaxis in surgical patients<sup>10</sup>.

Therefore we sought to determine the frequency and relative risk of venous thromboembolism in patients with malignancies. The association between cancer and VTE can be explained partly by the fact that cancer cells induce a hypercoagulable state thus facilitating cancer growth and metastasis<sup>11</sup>. The treatment of VTE is the administration of vitamin K antagonists and low molecular weight heparins<sup>12</sup>. According to one postulate anticoagulants may possess antineoplastic effects, when given for long-term prophylaxis<sup>13</sup>.

## MATERIAL AND METHODS

All patients presenting to Medical Oncology ward, Hayatabad Medical Complex, Peshawar from January 2010 to June 2011 were included in the study. Patients with malignancy associated DVT presenting to Surgical and Medical departments of Khyber Teaching Hospital Peshawar were also included in the

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study after being referred to Oncology Department Hayatabad Medical Complex. Inclusion criteria were malignancy with clinical symptoms and signs of DVT in the age range of 5 to 60 years. Total of 1200 patients were admitted during the study period. Biopsy proven malignancy was required for all patients. Routine baseline investigations including complete blood picture, biochemistry, ECG and X-rays were done on all patients. Diagnosis of DVT was based on history, physical examination and diagnostic ultrasonography. Taking into consideration the cost as well as availability of various diagnostic procedures, colour Doppler ultrasound complemented with real time B-mode ultrasound (duplex scanning) was carried out for the diagnosis of patients with suspected DVT.

Cerebral venous thrombosis was confirmed via Magnetic Resonance Venogram. Treatment protocol of patients diagnosed with DVT included Inj. Enoxaparin 1mg/Kg body weight subcutaneously twice daily for 5-7 days. Warfarin was started at the same time, and then continued for 4-6 months and longer periods, depending upon the non-resolution of the thrombus and activity of underlying malignancy.

## RESULTS

There were total 1200 admissions from January 2010 to June 2011. Thirty-five patients were found to have venous thromboembolism. This makes 2.9% of the total patients admitted during this time period to the oncology unit. Age distribution of the patients was 5-60 years, with mean age of 35 years. Gender distribution was 21 male patients 14 female patients. Primary cancer distribution is shown in Table 1. The Haematological malignancies with DVT is shown in Table 2.

Thirty-two patients had Doppler confirmed thrombosis in the femoro-popliteal system. One patient with Ca- esophagus and 1 with Burkitt's lymphoma had extensive bilateral leg DVT. Patient with chronic myeloid leukemia had cerebral venous thrombosis, confirmed on MRV (magnetic resonance venogram). Two patients with polycythaemia rubra vera had hepatic vein thrombosis confirmed via Doppler U/S of abdomen. Thirty two patients which makes 100% of those presenting with femoro-popliteal venous system thrombosis had the chief complaints of swelling of the affected limb and severe pain in the same limb. Redness of the affected limb was observed in twenty-four patients (70%).

Patient with cerebral venous thrombosis had severe headache and fundoscopy revealed bilateral papilloedema. Two patients with hepatic vein thrombosis with underlying polycythaemia rubra vera presented with severe abdominal pain. Examination revealed tender hepatomegaly with ascites in them.

**Table 1: Primary cancer distribution solid organs**

Solid Organ Tumors	Number of patients
Ca oesophagus	2
Ca colon	2
Ca ovary	6
Ca prostate	1
Osteosarcoma	1
Ca breast	3
Ca Bronchus	1
Rhabdomyosarcoma	1

**Table 2: Primary cancer distribution Haematological malignancies**

Haematological malignancies with DVT	No. of patients with DVT
Non-hodgkin's lymphoma	7
Burkitt's lymphoma	2
Acute myeloid leukemia	3
Multiple Myeloma	2
Chronic Myeloid Leukemia	1
Polycythaemia rubra vera	2
Myelofibrosis	1

**Table 3: Site of venous thrombosis**

Site	No. of patients and percentage
Unilateral leg DVT	30 (85.8%)
Bilateral Leg DVT	02 (5.7%)
Cerebral Venous Thrombosis	01 (2.9%)
Hepatic vein thrombosis	02 (2.9%)

All the patients were treated with inj. Enoxaparin 1mg/kg bodyweight subcutaneous twice daily for 5-7 days, along with concomitant administration of warfarin 5mg /day. Warfarin was continued for at least 6 months as per ACCP rules, with regular check up of INR (target INR between 2.5-3).

## DISCUSSION

Venous thrombosis, comprising deep vein thrombosis and pulmonary embolism, occurs with an incidence of approximately 1 per 1000 annually in adult population<sup>14</sup>. Risk is even higher in cancer patients<sup>15</sup>.

The Percentage of patients with cancer complicated by Venous thromboembolism is higher in the West as compared to our population i.e 15%-20% against 2.9% in the Asian population<sup>2</sup>. These results are supported by trials that also reveal a significantly lower incidence of thromboembolic disease in the Asian community. In Singapur recently, the incidence of sonographic evidence of DVT was found to be only three percent in the control group of patients undergoing colorectal surgery without receiving any form of prophylaxis<sup>16</sup>. Similarly, in another study reported from Faisalabad in 1991, only one out of hundred patients presented with sonographic evidence of DVT. None of them received any form of prophylaxis<sup>17</sup>.

Another study(during 2001-2002), was conducted in Pakistan Institute of Medical Sciences (PIMS), Islamabad, to evaluate the incidence of DVT in the posttraumatic hip, femur and knee surgery. Out of 100 patients 3 patients were found to have positive evidence on compression sonography conducted between 3<sup>rd</sup> and 10<sup>th</sup> postoperative days. However others believe this is chiefly due to scarcity of credible scientific evidence available regarding the magnitude of the risk of VTE present in this region<sup>18</sup>. The major outcomes of venous thrombosis are death, recurrence, post thrombotic syndrome and major bleeding due to anticoagulation<sup>19</sup>.

Major side effect of bleeding was not encountered in any patient when the INR was kept between 2.5-3. Our observation was different from reports of the West, which shows a 2-6 times higher incidence of bleeding complications with anticoagulant therapy in cancer patients<sup>10</sup>. It can partially be explained by the fact that our study period was limited to 18 months and the total number of patients with DVT was also low. Deranged or prolonged INR was an indication to withhold warfarin for sometime which was later on re-instituted at a lower dose, and continued.

The location of the thrombus was in consistence with world's literature. We found 2 patients with hepatic vein thrombosis in polycythaemia rubra vera. There is an association of active cancer and intra-abdominal DVT<sup>20,21</sup>. The incidence of DVT is believed to be lower in Asian population<sup>22</sup>. This is supported by studies of incidence rates in Asian countries as well as Asian minorities. One patient presented with cerebral venous thrombosis. He had underlying CML and presented with severe headache. Fundoscopy revealed bilateral papilloedema. CT Brain followed by MRV (Magnetic Resonance Venogram) confirmed the diagnosis.

The clinical diagnosis of deep vein thrombosis is notoriously unreliable. Confirmation is necessary before subjecting patients to the risk of long-term anticoagulation. Ascending venography was the reference standard for the diagnosis of DVT, but is

invasive and associated with adverse effects. Therefore venous duplex ultrasonography has become the routine initial evaluation of DVT. Ultrasonography or impedance plethysmography is sensitive and specific for the diagnosis of proximal occult venous thrombosis.

An abnormal result virtually confirms the diagnosis and treatment can begin. If a normal result is obtained but clinical suspicion remains high, then serial testing is indicated. Therefore Duplex and color Doppler Sonography is currently the technique of choice for diagnosis of DVT<sup>23</sup>.

Fibrin degradation products and D-dimers are considered useful for the diagnosis of thrombosis. However, the evidence for diagnosis of thrombosis by fibrin related products is not well established<sup>24</sup>. Considering the high sensitivity and specificity, positive and negative predictive value, we selected duplex ultrasound for diagnosis of femoro-popliteal and intra abdominal thrombosis. The diagnosis of cerebral venous thrombosis was confirmed via Magnetic Resonance Venogram, which is the gold standard<sup>25</sup>.

We started all the patients after confirmation of their diagnosis on low molecular weight Heparin (LMWH) for 5-7 days along with concomitant administration of oral warfarin 5-10mg per day. Warfarin was continued for 3-6 months. We observed good results with edema and pain subsiding within 5-10 days. We did not encounter any severe bleeding problems when the INR was kept in the range of 2.5-3.0.

## CONCLUSION

Antithrombotic agents reduce venous thromboembolism in patients with cancer undergoing either surgery or chemotherapy. Both low molecular weight heparins and low dose warfarin can prevent and treat thrombosis associated with malignancy. We recommend that venous thromboembolism should be initially treated with either Unfractionated Heparin (UFH) or a Low Molecular Weight Heparin (LMWH) followed by Warfarin therapy.

## REFERENCES

1. Brose KM, Lee AY. Cancer associated thrombosis: prevention and treatment. *Curr Oncol.* 2008 Jan; 15 (Suppl 1): 58-67.
2. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med.* 2006; 119(1): 60-68.
3. Khorana AA, Francis CW, Culakowa E, Kuderer WM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost.* 2007; 5(3): 632-34.

4. Blom JW, Vanderschoot JP, Ostindier MJ. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost.* 2006; 4(3): 529.
5. Ay C, Dunkler D, Marosi C. Prediction of venous thromboembolism in cancer patients. *Blood.* 2010; 116: 5377-82.
6. Khorana AA, Kuderer NM, Culakova E. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008; 111: 4902-7.
7. Khorana AA, Francis CW. Thrombolism in hospitalized neutropenic cancer patients. *J. Clin Oncol.* 2006, 24: 484-90.
8. Geerts WH, Bergqvist D, Pineo GF et al. Prevention of venous thromboembolism. American College of Chest Physicians Evidence- Based clinical practice guidelines. (8<sup>th</sup> Edition). *Chest:* 2008; 133(6 suppl): 381-453.
9. Nalluri SR, Chu D, Keresztes R, Zhu W. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta analysis. *JAMA* 2008; 19: 2277-85.
10. Kearon C, Kahn SR, Agnelli G et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest physicians Evidence based clinical practice guidelines chest 8<sup>th</sup> edition. 2008. 133; 454-545 .
11. Nijziel MR, Van Oerle R, Hilen HF, Hamulyak K: From Troussaeu to angiogenesis: the link between haemostatic system and cancer. *Neth J Med.* 2006; 64(11): 403-10.
12. Bochenek T, Nizankowski R. The treatment of venous thromboembolism with low molecular weight heparins, a meta analysis. *Thromb Haemost.* 2012 Apr; 107(4): 699-716.
13. Kuderer NM, Khorana AA, Lyman GH, Francis CF. A meta analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment: impact on survival and bleeding complications. *Cancer* 2007, 110: 1149-60.
14. White RH. The epidemiology of venous thrombo-embolism. *Circulation* 2003: 107(suppl 1): 14-18.
15. Croninfenton DP, Sandergaard F, LA Pederson LA, et al. Hospitalization for venous thromboembolism in cancer patients and the general population. A population based cohort study in Denmark, 1997-2006. *British Journal of Cancer* 2010. 103; 947-53.
16. HoYH, Seow C F, Leong A. Randomized controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian Patients, *Dis. Colon. Rectum.* 1999, 42: 196-203.
17. Khan K, Muhammad A, Pervaiz; Incidence of post operative DVT in our population using Doppler studies, SUR-279, Dissertation Index, College of Physicians and Surgeons of Pakistan, 1991: 4; 123-28.
18. Mirza W, Ashraf S, Fawad A. Role of routine use of thromboprophylaxis in patients undergoing major surgery. *Pakistan J. Med. Res.,* 2005. Vol. 44 No. 1. 21-26.
19. Kahn SR, Ducruet T, Lamping DL, Arsenault L et al. Prospective evaluation of health related quality of life in patients with deep venous thrombosis. *Arch Intern Med.* 2005. May 23; 165(10): 1173-78.
20. Martinelli I, Franchini M, Mannucci PM. How I treat rare venous thrombosis. *Blood* 2008. 112: 4818-23.
21. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thrombosis. *Clin Gastroenterol Hepatol.* 2010; 8(2): 200-05.
22. Karen PL. Yap and David R. Mc Cready. Deep Vein Thrombosis and Malignancy: A surgical oncologists perspective. *Asian Journal of Surgery* 2004, 27(3), 249-54.
23. Goodacre S, Stevenson M, Wailoo A, Sampson F, Sutton AJ, Thomas S. How should we diagnose suspected deep vein thrombosis. *QJM.* 2006; 99(6): 377-88.
24. Wada H, KobaYashi T, Abe Y. Elevated levels of soluble fibrin of d-dimer indicate high risk of thrombosis. *J Thromb Haemost* 2004 (2), 1256-60.
25. Tanislav C, Siekmann R, Allendofer J et al. cerebral vein thrombosis: clinical manifestation and diagnosis. *BMC Neurology* 2011, 10. 1471-77.