Indian J Med Res 130, December 2009, pp 726-730

A prospective study of risk factor profile & incidence of deep venous thrombosis among medically-ill hospitalized patients at a tertiary care hospital in northern India

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Received February 20, 2009

***Background & objectives*: Hospitalization for medical-illness is associated with an increased risk of deep venous thrombosis (DVT). However, there are no published data from India addressing at this issue. We sought to study the risk factor profile and the incidence of DVT among hospitalized medically-ill patients, a tertiary care hospital in northern India.**

***Methods*: All adults admitted to the medical wards and intensive care unit with level 1 or 2 mobility over a period of two years (July 2006 to July 2008) at the All India Institute of Medical Sciences hospital, New Delhi, were prospectively studied. Patients having DVT at admission or an anticipated hospital stay less than 48 h were excluded. The presence of clinical risk factors for DVT was recorded and laboratory evaluation was done for hypercoagulable state. A routine surveillance venous compression Doppler ultrasonography was performed 12 ± 8 days after hospital admission.**

***Results*: Of the 163 patients, 77 (47%) had more than one risk factor for DVT. Five (3%) patients developed DVT; none of them had symptomatic DVT. None of these patients received anticoagulation prior to the development of DVT. The mean age of those who developed DVT was 40 ± 13 (25-50) yr; two of five were male. The incidence rate of DVT was 2.7 per 1000 person-days of hospital stay [95% confidence interval (CI): 0.87 to 6.27]. None of the factors was found to be significantly associated with the risk of DVT.**

***Interpretation & conclusions*: In our setting, although many hospitalized medically-ill patients had risk factors for DVT, the absolute risk of DVT was low compared to the western population but clearly elevated compared to non hospitalized patients. Large studies from India are required to confirm our findings.**

Key words Deep venous thrombosis - intensive care unit - medical illness - pulmonary embolism - venous compression ultrasonography

Venous thrombosis represents a spectrum of diseases that includes both deep venous thrombosis (DVT) and pulmonary embolism[1]. Often, DVT is not suspected clinically leading to significant diagnostic delays. Venous thrombosis results in considerable, but potentially preventable, morbidity and mortality among hospitalized patients. Most of the hospitalized patients have a high risk of DVT, and hospitalization for acute

medical-illness is known to be associated with about eight-fold increased risk of DVT[2].

Because of the high rate of missed diagnosis, the true incidence of DVT is unknown. There is a lack of adequate studies on the incidence of DVT. Only a few studies exist published literature most of which were done on surgical patients. There are little published data available on the risk of DVT among hospitalized medically-ill patients. Hence, we sought to study the profile of risk factors and the incidence of DVT among medically-ill patients treated at a tertiary care hospital in northern India.

Material & Methods

Consecutive adults aged 18 yr or more admitted to the medical wards and intensive care unit with level 1 or 2 mobility over a period of two years from July 2006 to July 2008 at the All India Institute of Medical Sciences hospital, New Delhi, were prospectively included. Patients who had DVT at admission or an anticipated hospital stay less than 48 h, were excluded. The level of immobilization was defined as follows - level 1: total bed rest or sedentary patient; level 2: level 1 with bathroom privileges; and level 3: level 2 with activity as tolerated by the patient. A written informed consent was obtained from all patients participating in the study. The study protocol was reviewed and approved by the Institute Ethics Committee at the All India Institute of Medical Sciences, New Delhi

The data were collected on demographic details, primary diagnosis, and specific risk factors for DVT using a pre-designed data collection instrument. At enrollment, a general physical examination including a detailed examination of the lower limbs for signs of DVT was performed on all patients. In addition to evaluation of clinically suspected DVT or pulmonary thromboembolism as decided by the treating physician, a routine surveillance Doppler venous ultrasonography was performed on all patients. The venous ultrasonography was performed by one of the two consultant radiologists (AS and AK) using Philips HDI 5000® or Philips Envisor HD® sonographic units (Philips International B.V., Amsterdam, Netherlands). Examination was performed using a 7.5-10 MHz linear transducer with compression of deep veins of the thigh and calf in a sequential manner in 1 to 2 cm increments from the common femoral, superficial femoral, and popliteal veins. The lack of venous compressibility with the transducer held transverse to the artery and vein was interpreted as a positive study and was confirmed with color flow and pulsed wave Doppler analysis[3-5].

It was planned to perform a venous ultrasound within 24 h of admission and repeat it weekly for low-risk patients and twice-weekly for high-risk patients during the hospital stay. However, due to the large patient load on the radiology unit, the venous ultrasounds were performed once after 12 ± 8 days of hospitalization. A ProC® Global assay (Dade Behring, Marburg, GmbH) was performed on all patients to screen for abnormalities of the protein C/S pathway. Patients with a normalized ratio < 0.7 underwent further estimation of protein C and S and antithrombin levels in the plasma. Antithrombin was estimated by nephelometry using Turbox® antithrombin kit (Orion Diagnostica, Espoo, Finland); the lower limit of normal was 200 mg/l for this assay. Protein C and S levels were estimated by enzyme-linked immunosorbent assay (ELISA) using the REAADS® kit (Corgenix Inc., Colorado, USA). Lower limit of normal for protein C was 70 per cent and that for protein S was 60 per cent. In addition, estimation of IgM and IgG antiphospholipid antibodies by ELISA using the AESKULISA®Phospholipid-Screen-GM kit (Aesku Diagnostics GmbH) was done in all the patients.

The incidence rate of DVT was calculated assuming a Poisson distribution using a statistical software package (Intercooled stata 8.0 for windows, Stata Corp., College Station, Texas, USA). We compared the categorical data between groups by the Fisher's exact test and continuous variables by the independent samples t-test.

Results

A total of 163 patients contributing to 1860 person-days of observation were studied. None of the patients had a prior history of DVT. Table I summarizes the primary medical-illness necessitating hospitalization of these patients. All patients had immobilization as a risk factor for DVT. Other risk factors that were recorded included age, sex, duration of hospital stay, smoking, alcoholism, known hypercoagulable state, malignancy, haematological disorder, surgery, trauma, immobilization, intake of oral contraceptive pills, past history of DVT, varicose veins, central venous catheterization and use of mechanical ventilation. Of the 163 patients, 77 (47%) had more than one risk factor for DVT. Thirty four (21%) patients had two risk factors whereas three risk factors were present in 27 (17%) patients. Thirteen (8%) patients had four, two had five and one patient had seven risk factors for DVT. Regarding critical care risk factors, in total 45 (28%) received mechanical ventilation; of them two developed DVT. Mean duration of mechanical ventilation in patients who developed DVT was

10.5 days as compared to 6 days in patients who did not develop DVT. On surveillance, 5 (3%) of 163 patients were detected to have DVT (all proximal); none of them had symptomatic DVT. None of these patients received anticoagulation prior to the development of DVT. The demographic profile and risk factors in patients with and without DVT are presented in Table II. The mean age of those who developed DVT was 40 ± 13 (25-50) yr, and two were male. The incidence rate of DVT, calculated assuming a Poisson distribution, was 2.7 per 1000 person-days of hospital stay [95% confidence interval (CI): 0.87 to 6.27]. The results of laboratory evaluation for hypercoagulable state are presented in Table III. Hypercoagulability parameters were found to be positive in a comparatively higher percentage of patients with DVT. However, no factor was significantly associated with the risk of DVT.

Table I. Primary medical-illness necessitating hospitalization in the study population

Underlying disease*	Patients without DVT (n = 158)	Patients with DVT (n = 5)
Infectious diseases	97 (61)	3 (60)
Pulmonary infection	53 (33)	2 (40)
GI and liver infection	12 (8)	1 (20)
Genitourinary infection	4 (2)	-
CNS infection	8 (5)	-
Systemic infection	20 (13)	-
Malignancy	9 (6)	-
Chronic pulmonary disease	27 (17)	-
Cardiac disease	5 (3)	-
Rheumatic disease	21 (13)	-
Endocrine disease	4 (2)	-
Acute poisoning	3 (2)	1 (20)
Hematological disease	2 (1)	-
Hepatic disease	5 (3)	-
Neurological disease	6 (4)	-
Others	2 (1)	-
Psychiatric illness	-	1 (20)

Data presented as n (%); *, not mutually exclusive, some patients had multiple underlying diseases; DVT, deep venous thrombosis; GI, gastrointestinal; CNS, central nervous system

Table II. Demographic profile and risk factors in patients with and without DVT

Risk factor	Patients without DVT (n = 158)	Patients with DVT (n = 5)
Age, yr [mean ± SD (range)]	44 ± 18 (18-85)	40 ± 13 (25-50)
Male sex	86 (54)	2 (40)
Duration of hospital stay, days [mean ± SD(range)]	21.3 ± 12.2 (1-62)	33.5 ± 33.2 (10-30)
Smoking	54 (34)	2 (40)
Alcoholism	29 (18)	1 (20)
Known hypercoagulable state	0	0
Malignancy	11 (7)	0
Hematological disorder	4 (2)	1 (20)
Surgery	5 (3)	0
Trauma	9 (6)	0
Immobilization	158 (100)	5 (100)
Intake of OCPs	1	0
Past history of DVT	0	0
Varicose veins	1	0
Central venous catheterization	10 (6)	1 (20)
Mechanical ventilation	43 (27)	2 (40)

Data presented as n (%), unless specified; DVT, deep venous thrombosis; OCPs, oral contraceptive pills

Discussion

It was found that despite the high proportion of risk factors for DVT, only a small proportion of patients hospitalized for a medical-illness developed DVT. In earlier studies from western countries, the cumulative incidence of DVT among medical in-patients was found to be 10-20 per cent, and it was 10-80 per cent among critical care patients[6]. In a recent survey of hospitals from 32 countries worldwide, about 42 per cent of hospitalized medical patients were found to be at risk for venous thrombosis[7]. In the same study, a comparable proportion (45%) of medical in-patients in India was found to be at risk[7]. However, we did not find a statistically significant association between any of the clinical or laboratory risk factors and the development of DVT. This is most probably due to a lack of adequate statistical power in view of the very low number of patients who developed DVT.

As far as the incidence of DVT is concerned, most of the published studies from India[8-17] have reported a low incidence of DVT among hospitalized patients (Table IV). However, all these studies were carried out on surgical or orthopedic patients, and ours is the first attempt from India to find out the incidence of DVT in hospitalized medically-ill patients. The risk of DVT was clearly elevated in hospitalized patients

Table III. Laboratory evaluation for hypercoagulability in patients with and without DVT

Laboratory abnormality	Patients without DVT (n = 158)	Patients with DVT (n = 5)
Pro C® Global < 0.7	53 (33)	1 (20)
IgM antiphospholipid antibody-positive (>15 IU)	4 (2)	1 (20)
IgG antiphospholipid antibody-positive	1	0
Antithrombin < 200 mg/l	4 (2)	0
Protein C < 70%	26 (16)	2 (40)
Protein S < 60%	36 (23)	2 (40)

Data presented as n (%); DVT, deep venous thrombosis

Table IV. Studies from India on incidence of DVT among hospitalized patients

Study	Study design	Study population	No. of patients studied	Incidence of DVT (%)
Shead *et al*[8]	Prospective	Surgical	50	28
Sharma *et al*[9]	Prospective	Orthopedic	112	19.6
Agarwala *et al*[10]	Prospective	Orthopedic	104	60
Jain *et al*[11]	Prospective	Orthopedic	72	2.7
Bhan *et al*[12]	Prospective, multicentric	Orthopedic	30	23.3
Leizorovicz *et al*[13]	Prospective, international, multicentric	Orthopedic	2420*	2.3
Maini *et al*[14]	Retrospective	Orthopedic	271	9.9
Saraf *et al*[15]	Prospective	Orthopedic	70	10
Mavalankar *et al*[16]	Prospective	Orthopedic	125	7.2
Kakkar *et al*[17]	Autopsy-based	Medical in-patients	1000 autopsies	15.9†
Present study	Prospective	Medical indoor patients	163	3

DVT, deep venous thrombosis; *, conducted in 39 centers in 11 Asian countries including 403 patients from nine centers in India; †, pulmonary embolism diagnosed at autopsy, not DVT

in our study compared to non hospitalized patients, where risks were around 1.5 per 1000 person-years[18]. Our study results are in contrast to earlier studies from western countries and reinforce the repeated finding of a low incidence of DVT among surgical patients in India. However, a large autopsy-based study from India had found a high prevalence (16%) of pulmonary embolism at autopsy in patients dying of a medical-illness[17]. The significance of this isolated autopsy-based study in the face of mounting evidence to the contrary is unclear.

The diagnosis of DVT is often not suspected clinically, and there is a possibility of underdiagnosis. Therefore, venous compression ultrasonography was performed for all patients irrespective of the clinical suspicion. Doppler analysis has emerged as a sensitive and accurate non-invasive test for confirming the presence of acute DVT[19]. Its sensitivity and specificity for the diagnosis of symptomatic proximal DVT are 97 and 94 per cent, respectively. Therefore, although ascending contrast venography is considered the gold standard for the diagnosis of DVT, the method employed to diagnose DVT in the present study is an acceptable alternative, and this is unlikely to be the reason for the low incidence of DVT in the present study.

Our study has its merit in being a prospective study, and we included consecutive adults hospitalized for a medical-illness both to the medical wards and the ICU. Thus, our study population faithfully reflects the clinical spectrum of illness encountered by a physician in a typical tertiary care set-up. Patients in a tertiary care set-up are likely to be sicker and possibly are at a comparatively higher risk of DVT than patients treated at the secondary care level. Notwithstanding this possibility, we found a low incidence of DVT in our study population. The limitation of our study was that venous ultrasonography could not be performed as planned due to operational constraints.

The obvious question that arises now is why only a small number of our patients developed DVT as compared to the western population despite apparently being at comparable risk. Our study was not addressed at this question, and this deserves further research. Inclusion of symptomatic cases in some of these studies could explain the difference from our study. Another possible explanation is the difference in the genetic make up of the population. Irrespective of the reason for this difference, the results of our study and most other Indian studies on surgical patients question the advisability of routine use of thromboprophylaxis in hospitalized medically-ill patients which is now considered the standard-of-care in western countries. Further large studies from India are needed to confirm the findings of the present study.

Acknowledgment

This study was supported by an unrestricted educational grant from Pfizer India Ltd. to SKS. The sponsor played no role in the study design, data collection, analysis, or the decision to submit for publication.

Conflicts of interest: SKS participated as an investigator in the EXCLAIM and LIFENOX clinical trials sponsored by Sanofi Aventis. TK was a co-investigator in the LIFENOX clinical trial sponsored by Sanofi Aventis.

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