Research Article

Prophylaxis and Incidence of Symptomatic Deep Vein Thrombosis in Indian Patients with Sepsis: DETECT-Deep Vein Thrombosis Registry

Nagarajan Ramakrishnan, DETECT-DVT Investigators*

Department of Critical Care Medicine, Apollo Hospitals, Chennai, Tamil Nadu, India

Abstract

Purpose: To assess thromboprophylaxis rate and incidence of symptomatic deep vein thrombosis (DVT) in Indian patients with acute sepsis. **Materials and Methods:** Adult patients with sepsis, within 48 h of sepsis onset/hospital admission were included. DVT was assessed using Doppler ultrasonography if clinical signs were present. Data were collected at inclusion, discharge, and 30 ± 7 days (if discharged before 30 days). **Results:** The study included 278 patients (men: 69.4%; mean age: 56.3 ± 17.99 years). Out of 275 patients (data missing for 3 patients), 188 (68.4%; 95% confidence interval: 62.5–73.8) received DVT prophylaxis (185 at admission and 3 at discharge; pharmacological prophylaxis: *n* = 88, mechanical prophylaxis: *n* = 65, pharmacological + mechanical prophylaxis: *n* = 35) and 87 received no prophylaxis. In line with American College of Chest Physicians 2008 recommendations, among patients who received pharmacological prophylaxis (*n* = 123), low-molecular-weight heparin was given to 85.4% (*n* = 105) patients (duration: 9.1 ± 6.36 days), unfractionated heparin to 12.2% (*n* = 15) patients (duration: 9.2 ± 9.18 days), and fondaparinux to 5.7% (*n* = 7) patients (duration: 6.8 ± 3.30 days); 27/63 patients at high-risk of bleeding received mechanical prophylaxis; no patient received aspirin. Of 9 patients who developed DVT, 7 received no thromboprophylaxis (data missing for 2 patients). In total, 186/274 (67.9%) patients recovered from sepsis. **Conclusions:** Two-third patients received thromboprophylaxis. The substantial role of thromboprophylaxis in DVT prevention mandates monitoring and control of thromboprophylaxis through internal audits in hospitals.

Keywords: Doppler ultrasonography, heparin (low molecular weight), Indian study (prospective), sepsis, venous thrombosis

Introduction

Sepsis, one of the oldest and most elusive syndromes, exhibits high mortality rates and is the most common cause of death among critically ill patients in noncoronary Intensive Care Units (ICUs).[1,2] In a multicenter, prospective, observational study conducted in intensive therapy units in India, the incidence of severe sepsis was 13.1% of all admissions.[3]

Sepsis leads to complications in coagulation and may manifest from mild alterations to severe disseminated intravascular coagulation.[4] In sepsis, toxins activate coagulation directly through the effect of chemical mediators on endothelium and monocytes. In addition, pro-inflammatory cascade can result in indirect coagulation. Sepsis-induced procoagulant activity is more severe than that produced by trauma.[5] Severe sepsis predisposes patients toward venous thromboembolism (VTE) due to risk factors such as advanced age, chronic cardiopulmonary disease, recent surgery, immobilization, in-dwelling vascular catheters, and previous VTE history. Thromboembolic complications contribute to the burden of severe sepsis and are observed in approximately one out of every 32 severe sepsis patients.[6]

The international guidelines recommend deep vein thrombosis (DVT) prophylaxis with either twice or thrice daily low-dose unfractionated heparin (UFH) or daily low molecular weight heparin (LMWH) in patients with severe sepsis unless contraindicated (i.e., thrombocytopenia, severe coagulopathy,

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Address for correspondence: Dr. Nagarajan Ramakrishnan, Department of Critical Care Medicine, Apollo Hospitals, 21 Greams Lane, Off Greams Road, Chennai - 600 006, Tamil Nadu, India.
E-mail: ram@icuconsultants.com

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active bleeding, and recent intracerebral hemorrhage). Moreover, patients with a contraindication for heparin should receive mechanical prophylactic devices such as graduated compression stockings (GCS) or intermittent compression devices. Similarly, a combination of pharmacologic and mechanical therapy should be used in very high-risk severe sepsis patients with a history of DVT, trauma, or orthopedic surgery unless contraindicated or not practical. In addition, owing to proven superiority of LMWH in high-risk patients, it should be preferred over UFH.[7] Subcutaneous heparin reduces the risk of thromboembolic events from 29% to 13% in ICU patients.[8] In a randomized prospective study, UFH significantly reduces mortality compared to no treatment (7.8% vs. 10.9%).[9]

The VTE prophylaxis is suboptimal in Asia due to a misconception that the incidence of VTE is lower in Asians than Caucasians; however, several studies have negated this belief.[10-12] A dearth of well-designed multicenter trials and discrepancies in the reported incidences have resulted in an underestimation of DVT incidence in the Indian population.[10,11] The Asian VTE guidelines recommend a formal hospital VTE protocol for risk assessment and prophylaxis to dispel myths and institute a clear clinical pathway for the clinicians and hospital staff.[10] Periodic studies assessing DVT incidence and thromboprophylaxis rates in India are essential for the development of strategies to improve the management of thromboprophylaxis.

The primary objective of this study was to determine the proportion of patients with sepsis who were given thromboprophylaxis. The secondary objectives were to determine the proportion of patients with sepsis developing DVT at discharge and to compare how many of these patients had received DVT prophylaxis, to evaluate the profile of patients admitted with sepsis, to determine the treatment for sepsis employed by the investigator in relation to thromboprophylaxis and antibiotic use, the outcome of sepsis, and DVT prophylaxis rate according to American College of Chest Physicians (ACCP) guidelines.

Materials and Methods

This was a prospective observational study conducted in accordance with the guidelines for Good Epidemiology Practice. Each participating site had taken all necessary permissions to conduct this study.

Inclusion and exclusion criteria

Adult inpatients with sepsis (including patients with severe sepsis and septic shock), from whom signed informed consent was obtained before initiation of the study (day of inclusion was considered to be within 48 h of onset of sepsis or within 48 h of current admission), were included. Patients who had participated in any clinical trial in the past 1 month were excluded.

Definitions

According to the International Guidelines for Management of Severe Sepsis and Septic Shock, 2012, sepsis was defined as the systemic response to infection, manifested by two or more of the following conditions as a result of infection:

1. Temperature >38°C or <36°C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or partial pressure of carbon dioxide in arterial blood (PaCO), <32 mmHg; and white blood cell count >12,000 cmm or <4000/cu mm, or >10% immature (band) forms.[13]

Severe sepsis referred to sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities included but were not limited to lactic acidosis, oliguria, or an acute alteration in mental status.[13]

Septic shock in adults referred to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.[14]

Data collection

At baseline (visit 1), patients satisfying the eligibility criteria were enrolled; their profile and the treatment modalities for sepsis along with DVT prophylaxis were recorded. Patients were assessed for the presence of DVT symptoms such as pain, swelling, and redness of the leg and dilatation of the surface veins at visit 1(baseline visit) and visit 2 (discharge)/ visit 3 (30 ± 7 days; if the patient was discharged after 30 days, data at visit 3 were not considered). Patients with these symptoms were evaluated for DVT using Doppler ultrasonography. Treatment modalities and the outcome of the sepsis were recorded. Data were transcribed from source documents (patient file, prescription letters, or any other relevant document) to case report forms.

Statistical analysis

Sample size: Assuming that 20% of the patients with sepsis would be given thromboprophylaxis, with a 90% confidence interval (CI) and 4% precision, 269 patients were required for the study. Accounting for a drop-out of 20%, 340 patients were required.

Descriptive statistics were done on patient characteristics and endpoints. Based on type of each variable (quantitative or qualitative), number of patients, means, standard deviations, percentages, and number of missing data were presented. Baseline characteristics were compared between patients with and without thromboprophylaxis, using Chi-square tests. $P < 0.05$ was considered as significant. Statistical analysis was performed by Makrocare using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition

A total of 278 patients were recruited from 23 sites across India; 183 patients completed the study, while 91 patients discontinued the study for various reasons and data on study completion were missing for 4 patients. Of the 91 patients who did not complete

study, one patient withdrew consent (only baseline data was analyzed for this patient), while the other 90 were included in the data analysis set of 278 patients. Death (60.4%, 55/91) was the major cause of discontinuation, followed by discharge against medical advice (30.8%, 28/91) [Figure 1].

Demographics and clinical characteristics

The mean age was 56.3 ± 17.99 years, and the majority (n = 193, 69.4%) were men. Among the 275 patients with sepsis, majority (n = 127, 46.2%) had sepsis that was not severe and was without septic shock, followed by severe sepsis (n = 94, 34.2%) and septic shock (n = 54, 19.6%). Majority of patients (85.3%, 237/278) were admitted in corporate hospital with most patients (59.4%, 165/278) in hospitals with >301 beds. The mean duration of hospital stay was 15.7 ± 13.78 days [Table 1].

Proportion of patients receiving thromboprophylaxis

Of the 68.4% (188/275; 95% CI: 62.5–73.8) patients who received thromboprophylaxis, 65.4% (123/188; 95% CI: 58.1–72.2) received pharmacological and 53.2% (100/188; 95% CI: 45.8–60.5) received mechanical thromboprophylaxis [Table 2]. About 46.8% patients (88/188; 95% CI: 39.5–54.2) received pharmacological alone; 34.6% (65/188; 95% CI: 27.8–41.8) received mechanical alone; 18.6% (35/188; 95% CI: 13.3–24.9) received both pharmacological and mechanical thromboprophylaxis. The main reason cited for not giving thromboprophylaxis was "Patient recovered" (pharmacological – 63.2%, 96/152; mechanical – 57.1%, 100/175) [Figure 2].

A high proportion of patients in the septic shock (74.1%, 40/54), severe sepsis (83.5%, 76/91), and sepsis that was not severe and without septic shock (55.1%, 70/127) groups received thromboprophylaxis. Thromboprophylaxis was predominantly given to patients belonging to ≥61 years age group (79.2%, 95/120) in metro noncorporate hospitals (78.6%, 11/14). Among patients receiving

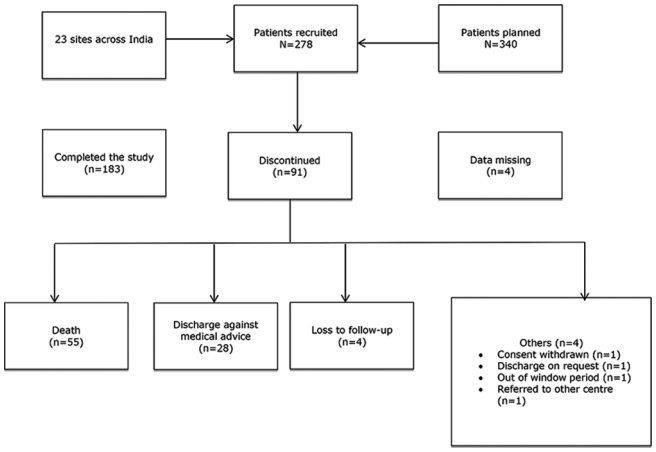

Figure 1: Patient disposition. n: Number of patients

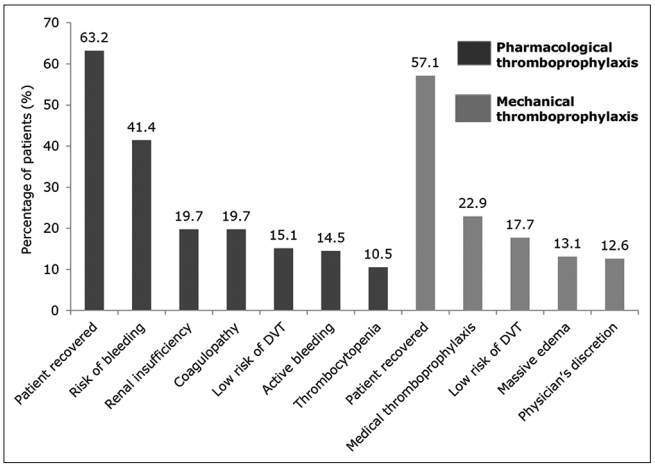

Figure 2: Major reasons for not administering pharmacological and mechanical thromboprophylaxis. DVT: Deep vein thrombosis

Table 1: Baseline characteristics, overall and according to thromboprophylaxis administration

Variable	n (%)	Thromboprophylaxis given (n=188)	Thromboprophylaxis not given (n=87)	Missing	P
Age (years)					
≤40	54	31 (57.4)	23 (42.6)	1	0.0031[a]
41-60	99	61 (61.6)	38 (38.4)	1	-
≥61	120	95 (79.2)	25 (20.8)	1	-
Gender					
Male	192	131 (68.2)	61 (31.8)	1	0.9419[a]
Female	83	57 (68.7)	26 (31.3)	2	-
Sepsis (n=275)					
Severe sepsis	91 (34.2)	76 (83.5)	15 (16.5)	3	<0.0001
Septic shock	54 (19.6)	40 (74.1)	14 (25.9)	0	-
Sepsis, not severe without septic shock	127 (46.2)	70 (55.1)	57 (44.9)	0	-
Type of hospital					
Rural hospital	27 (9.7)	14 (51.9)	13 (48.1)	0	0.1189
Metro corporate hospital	237 (85.3)	63 (69.7)	71 (30.3)	3	-
Metro noncorporate hospital	14 (5.0)	11 (78.6)	3 (21.4)	0	-

[a]Chi-square test was used to calculate the P value. -: Not available

thromboprophylaxis, 185/188 patients received it at visit 1 (baseline) while 3/188 patients received it at visit 2 (discharge). The baseline profile (in terms of age and stage of sepsis) was significantly different for patients who were given than those not given thromboprophylaxis [Table 1].

Pharmacological thromboprophylaxis

LMWH (85.4%, 105/123; mean dose: 41.1 mg/day; mean duration: 9.1 ± 6.36 days) was the most commonly used pharmacological prophylaxis followed by UFH (12.2%, 15/123; mean dose: 9204.5 IU/day; mean duration: 9.2 ± 9.18 days), fondaparinux (5.7%, 7/123; mean dose: 2.5 mg/day; mean duration: 6.8 ± 3.30 days), and oral warfarin (0.8%, 1/123; mean dose: 7.5 mg/day) [Table 2]. LMWH, UFH, and fondaparinux were administered subcutaneously.

Mechanical thromboprophylaxis

Intermittent pneumatic compression (68.0%, 68/100) was the most common form of mechanical compression followed by GCS (29%, 29/100) [Table 2].

Proportion and clinical profile of patients who developed deep vein thrombosis

In total, 9/278 (3.2%) patients developed DVT; of them, 7 were not given thromboprophylaxis and data were missing for 2 patients. None of the patients receiving thromboprophylaxis developed DVT [Figure 3]. Of 9 patients who developed DVT, 6 were treated with LMWH alone, and 2 received LMWH and warfarin, and data were missing for 1 patient. Among the 9 patients with DVT, 4 were in the age group of 41–60 years, 6 were women, and 4 had severe sepsis at baseline; also, 5 patients were admitted in metro corporate hospitals while 4 in rural hospitals.

Antibiotics used

Major antibiotics and corresponding mean duration of use were piperacillin-tazobactam (27.9%, 74/265; 8.3 ± 5.52 days), meropenem (26.8%, 71/265; 8.1 ± 5.97 days), levofloxacin (17.0%, 45/265; 7.5 ± 3.77 days), metronidazole (15.8%, 42/265; 7.6 ± 2.84 days), and cefoperazone-sulbactam (13.6%, 36/265; 6.5 ± 4.38 days).

Table 2: Type and duration of thromboprophylaxis (*n*=188)

Category[a]	*n* (%)	Duration of treatment, days (mean±SD)
Pharmacological thromboprophylaxis given	123 (65.4)	-
LMWH	105 (85.4)	9.1 (6.36)
UFH	15 (12.2)	9.2 (9.18)
Fondaparinux	7 (5.7)	6.8 (3.30)
Other	1 (0.8)	-
Oral warfarin	1 (0.8)	-
Mechanical thromboprophylaxis given	100 (53.2)	-
Graduated compression stockings	29 (29.0)	11.2 (6.68)
Intermittent pneumatic compression	68 (68.0)	13.1 (13.40)
Other	6 (6.0)	-
Deep vein thrombosis stockings	1 (1.0)	-
Thromboembolic deterrent stockings	5 (5.0)	-

[a]Some patients were administered more than one type of mechanical thromboprophylaxis. -: Not available; SD: Standard deviation; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin

Outcome of sepsis

At discharge, 186 (67.9%) patients had recovered from sepsis, and 88 (32.1%) did not recover from sepsis (data missing = 4). Among patients who did not recover, 55/88 (62.5%) died, 28/88 (31.8%) were discharged against medical advice, 1/88 (1.1%) was referred to some other center, 1 (1.1%) was discharged on request, and data were missing for 3 patients.

Among 126 patients with nonsevere sepsis and who had no septic shock, 101 (80.2%) had recovered and 25 (19.8%) had not recovered. Similarly, out of 92 patients who had severe sepsis at baseline, 55 (59.8%) had recovered and 37 (40.2%) had not recovered. In 53 patients who had septic shock at baseline, 28 (52.8%) had recovered and 25 (47.2%) had not recovered.

Evaluation of deep vein thrombosis prophylaxis according to American College of Chest Physicians guidelines

1. For acutely ill patients with sepsis, ACCP recommends LMWH, UFH, or fondaparinux
   - Pharmacological prophylaxis was given to 123/188 patients (65.4%). LMWH (105/123, 85.4%) was the most used pharmacological thromboprophylaxis followed by UFH (15/123, 12.2%) and fondaparinux (7/123, 5.7%).
2. ACCP recommends mechanical methods of thromboprophylaxis in patients at high risk of bleeding. Out of 63 patients with risk of bleeding, 27 (42.9%) received mechanical thromboprophylaxis, 5 (7.9%) received both pharmacological and mechanical thromboprophylaxis, and 36 (57.1%) received neither pharmacological nor mechanical thromboprophylaxis
3. ACCP recommends against the use of aspirin alone as thromboprophylaxis for any patient group.

None of the patients received aspirin.

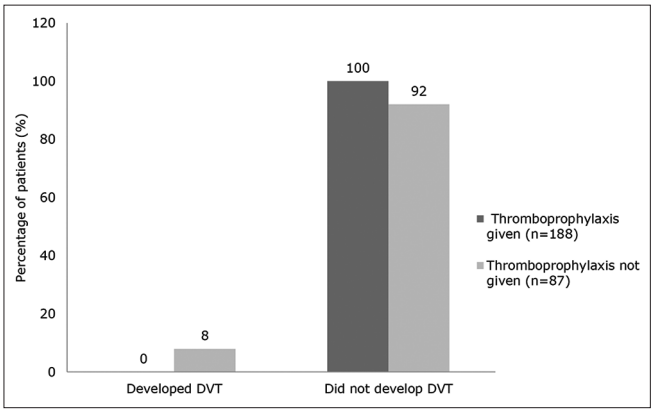

Figure 3: DVT development with respect to thromboprophylaxis administration. DVT: Deep vein thrombosis

Discussion

This prospective observational study recruited 278 patients from 23 sites across India. Majority of the patients (46.2%) had sepsis, which was not severe and without septic shock, followed by severe sepsis (34.2%) and septic shock (19.6%). Most patients (68.4%) received thromboprophylaxis. None of the patients who received DVT prophylaxis developed DVT (9 patients developed DVT, out of which 7 patients were not given thromboprophylaxis and data on 2 patients were missing). Of 9 patients who developed DVT, 6 were treated with LMWH alone and 2 received LMWH and warfarin as DVT treatment. Most patients with sepsis at baseline recovered; highest proportion of patients recovered in the group where the stage of sepsis was not severe, and patients had no septic shock. The rate and method of DVT prophylaxis was largely in line with the ACCP guidelines, except for the large proportion of patients with high risk of bleeding (57.1%, 36/63) who did not receive any prophylaxis.

Proportion of patients given thromboprophylaxis

The high risk for developing DVT seen in India makes it imperative to aggressively provide thromboprophylaxis unless contraindicated.[15] In CURVE (Multi-Centre Chart Audit of the Utilization of Risk Assessment and Prophylaxis of VTE in Acutely Ill Medical Patients in Canada), a national, multicenter thromboprophylaxis audit conducted in Canada, about 23% patients received thromboprophylaxis.[16] In another prospective epidemiological observational study by ANZIC (Australian and New Zealand Intensive Care Society) center, a thromboprophylaxis rate of 86% was observed.[17] A review of the records of consecutive admissions to the medical ICU at Stanford and an affiliated Veterans Affairs hospital showed that 75% patients received thromboprophylaxis.[18] A prospective observational study conducted in the ICU and wards in a tertiary care center in India showed a low DVT prophylaxis rate of 12.5%.[15] In our study, 68.4% patients received thromboprophylaxis. These variations in the thromboprophylaxis rates could be due to different practices followed across varied clinical settings and differential level of compliance with international guidelines.

In this study, 65.4% patients received pharmacological thromboprophylaxis and 53.2% patients received mechanical thromboprophylaxis. A review of the records of all medical admissions to the ICUs of a university hospital in California showed about 20% patients receiving pharmacological prophylaxis, 38% receiving mechanical prophylaxis, and 18% receiving prophylaxis by both methods.[18] In an epidemiological audit of venous thromboprophylaxis management in critically ill patients including those with severe sepsis conducted by ANZIC center, 64% patients received pharmacological prophylaxis and 80% patients received mechanical prophylaxis.[17] The differential proportion of patients receiving a particular type of thromboprophylaxis could be attributed to diversity in risk factors and their combinations observed in these patient groups. In this study, "Patient recovered" was the main reason for not administering pharmacological and mechanical prophylaxis, which indicates that thromboprophylaxis is not being considered early in patients with sepsis. The American Society of Health-System Pharmacists suggests initiating thromboprophylaxis within 24 h of admission to the hospital.[19] This highlights the suboptimal adherence to thromboprophylaxis guidelines and calls for their stricter implementation.

Patients with deep vein thrombosis and association with thromboprophylaxis

A historical cohort study examining all cases of DVT and pulmonary embolism during 1996–1997 at a large teaching hospital found that 1 in 6 cases of symptomatic VTE could be avoided with adequate administration of prophylaxis.[20] This finding is corroborated by our study, where none of the patients who received thromboprophylaxis developed DVT. In an observational study done in a tertiary healthcare center in North India, Pandey *et al*. found a 25.8% prevalence of DVT (based on clinical signs and symptoms).[15] However, in our study, 9 (3.2%) patients developed symptomatic DVT. This difference could be due to major (85.3%) recruitment from corporate hospitals (which might tend to have sepsis protocol for early detection and treatment in place), and thereby higher thromboprophylaxis rates in our study (68.4%) compared to the earlier study (12.5%).

Outcome of sepsis

In total, 186 (67.9%) patients had recovered from sepsis at discharge; among those who did not recover, 55/88 (62.5%) patients died. In a study involving 175,665 patients admitted to 134 ICUs in Australia and New Zealand, the omission of thromboprophylaxis within the first 24 h of ICU admission without obvious reasons resulted in an increased risk of mortality in critically ill adult patients which included sepsis patients. The association between the omission of early thromboprophylaxis and hospital mortality was particularly strong for patients with sepsis (OR, 1.52; 95% CI, 1.27–1.81).[21] Further, a study of the records at medical ICU at Stanford and an affiliated Veterans Affairs hospital showed that the odds of death were 55% lower in patients receiving pharmacological prophylaxis compared with those receiving mechanical prophylaxis alone or no prophylaxis (odds ratio, 0.45; 95% CI: 0.22–0.93; $P = 0.03$).[18] Thus, the available evidence indicates that early and adequate initiation of thromboprophylaxis plays an important role in mortality rates in patients with sepsis.

Evaluation of deep vein thrombosis prophylaxis according to American College of Chest Physicians guidelines

For acutely ill medical patients admitted to hospital with sepsis, ACCP recommends thromboprophylaxis with LMWH, UFH, or fondaparinux. In our study, among those who received pharmacological thromboprophylaxis, 85.4%, 12.2%, and 5.7% were given LMWH, UFH, and fondaparinux, respectively; whereas in other studies, more patients received UFH over LMWH (73% vs. 24%).[17,18] The Surviving Sepsis Campaign recommends the use of LMWH daily for thromboprophylaxis

instead of UFH twice daily,[22] may be because hemorrhagic complications and pulmonary emboli incidences are shown to be less in patients who are administered with LMWH.[23-25]

Using mechanical prophylaxis reduces the risk of DVT by about two-thirds as monotherapy and by about half in combination with a pharmacological method.[26] ACCP recommends mechanical thromboprophylaxis, primarily, in patients at high risk of bleeding. In this study, out of 63 patients with risk of bleeding, 42.9% received mechanical thromboprophylaxis, 7.9% received both pharmacological and mechanical thromboprophylaxis, and 57.1% did not receive any thromboprophylaxis. ACCP recommends against the use of aspirin alone as thromboprophylaxis for any patient group. Conforming to the ACCP guidelines, none of the patients received aspirin as thromboprophylaxis. The available evidence suggests that decisions regarding the type of prophylaxis should be based on risk factors for both thrombosis and bleeding, clinical context, and patients' values and preferences.[23]

Strengths and limitations

The study included patients from 23 sites across India (six from North, seven from South, three from East, and seven from West) and thus was representative of the diverse geographical population across the country. A prospective study design enabled collection of follow-up data on the outcome of sepsis. However, the study was subject to the shortcomings of observational studies such as confounding factors. The study centers included may have increased awareness about the use of VTE prophylaxis, thus impacting the rate of thromboprophylaxis. Furthermore, centers willing to participate may have different standards or practices than that of others. Patients were not evaluated for the presence of pulmonary embolism, which could be an important cause of death seen in this study. Only the presence of symptomatic DVT was assessed in patients with sepsis; further studies evaluating the prevalence of asymptomatic DVT in patients with sepsis would be required.

Conclusions

VTE represents one of the most crucial illnesses in patients with sepsis and is often overlooked and considered as an outcome of hospitalization, rather than a full-fledged disease entity. Given the substantial role of thromboprophylaxis in VTE prevention, internal audits in hospitals to monitor and control the process of thromboprophylaxis should be encouraged. The morbidity and mortality associated with VTE call for intensified efforts in identifying and addressing factors responsible for nonadherence to international guidelines and implementing strategies to promote compliance.

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Conflicts of interest

Nil.

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Annexure

* Following is the list of the DETECT-DVT Investigators

Dr. Mohammed Faruk H. Memon, Ahmedabad;
Dr. Mayur Patel, Mumbai; Dr. Kedar Toraskar, Mumbai;
Dr. Leena Shah, Pune; Dr. Rajan Barokar, Nagpur;
Dr. Manish Jain, Mumbai; Dr. Sanjay Dhanuka, Indore;
Dr. V. K. Thakur, Bihar; Dr. Himjyoti Das, Meghalaya;
Dr. Animesh Gupta, Dr. Raymond Dominic Savio, Kochi;
Dr. V. N. Rajasekaran, Madurai; Dr. K. VijilRahulan,
Chennai; Dr. P. C. Vijaya Kumar; Chennai;
Dr. Ashwin K. Mani, Chennai; Dr. Chetan Goel, Mohali;
Dr. Amit Bery, Punjab; Dr. Naveen Gupta, Ludhiana;
Dr. Sandeep Diwan, New Delhi; Dr. Prakash Shastri,
New Delhi; Dr. Omender Singh, New Delhi;
Dr. Suhasini Tirumala, Secunderabad.