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A Prospective Observational Study of Venous Thromboembolism Prophylactic Therapy in Tertiary Care Hospital

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ABSTRACT

The aim of the study was to analyze the use of drugs in prophylaxis of venous thromboembolism in a tertiary care hospital.This study was carried out for duration of 6 months at the Inpatient department of General medicine in Osmania general hospital, Afzalgunj, Hyderabad. The data of 100 patients was collected, risk associated with VTE are verified as per Modified Padua Prediction score and prophylactic therapy given was evaluated as per ACCP Guidelines and, if any, deviations were noted.The study identified several risk factors associated with an increased risk of VTE, with reduced mobility being the most common. Further prevalent risk factors identified by this which were statistically significant are acute MI, ischemic stroke and post-operative status. 70% of the patients at the risk of VTE were managed with antiplatelets, while the rest 30% received oral or parental anticoagulants. The prophylaxis guidelines were followed in 65% of the patients. The reasons for inappropriate therapy were found to be prescribing aspirin as monotherapy and not giving any therapy to high risk patients.Despite the existence of several guidelines, some of them recently updated, adequate thromboprophylaxis therapy is not being prescribed. Thus, it reinforces the need for further investigation into developing of VTE in hospitalized patients, including identification of high-risk patients and appropriate thromboprophylaxis strategies.

KEYWORDS: Prophylaxis, Tertiary, Post-Operative, Anticoaugulants, Thromboprophylaxis

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1. INTRODUCTION

A blood clot that forms within a vein is called Venous Thromboembolism (VTE). The most common type of VTE is Deep Vein Thromboembolism (DVT), which is a blood clot in the deep vein of the legs. If the thrombus breaks off and flows towards the lungs, it is called as pulmonary embolism (PE), a blood clot in the lungs.[1]

There is a prevailing belief that deep vein thromboembolism in the ASIAN population is less than that in the western population, this has been disapproved by recent studies and there appears no reason that this is not same in India. The incidence of VTE in India is highly underestimated due to lack of adequate studies highlighting the incidence of VTE especially in medical patients, existence of a few but conflicting studies in post-surgical patients and deficiency of data from autopsied patients, as autopsies are being done in very few institutions in India.[2]

1.1prevention

Evidence supports use of heparin in people following surgery who have a high risk of thrombosis to reduce the risk of DVTs; however, the effect on PEs or overall mortality is not completely known. In hospitalized non-surgical patients, mortality does not change. It does not however decrease the rate of symptomatic DVTs. Using both heparin and compression stockings seems to be better than either one alone in reducing the rate of DVT.

In hospitalized people who have had a stroke and not had surgery, mechanical measures (such as compression stockings) resulted in skin damage and no clinical improvement. Data on the effectiveness of compression stockings among hospitalized non-surgical patients without stroke is less. [3]

The American College of Chest Physicians (ACCP) have given three strong recommendations with moderate quality evidence on VTE prevention in non-surgical patients: a) hospitalized patients be assessed for their risk of thromboembolism and bleeding before prophylaxis (prevention); b) heparin or a related drug is used if potential benefits are thought to outweigh potential harms; and c) graduated compression stockings not be used. As an ACP policy implication, guideline stated a lack of support for any performance measures that incentivize physicians to apply universal prophylaxis without regard to the risks. Goldhaber recommends that people should be assessed at their hospital discharge for persistent high-risk of venous thrombosis, and that people who adopt a heart-healthy lifestyle might lower their risk of venous thrombosis.

In patients with cancer who are still walking, about yet receiving chemotherapy, LMWH decreases the risk of VTE. Due to potential concerns of bleeding its routine use is not recommended. For people who are having surgery for cancer, it is recommended that they receive

anticoagulation therapy (preferably LMWH) to prevent a VTE. LMWH is recommended for at least 7–10 days following cancer surgery, and for one month following surgery for people who have a high risk of VTEs.

In adults who have had their lower leg casted or placed in a brace for more than a week, LMWH decreased the risk of VTEs. LMWH is recommended for adults not in hospital with an above-knee cast and a below-knee cast and is safe for this indication.

Following the completion of warfarin in those with prior VTE, long term aspirin is beneficial.

ACCP Recommendations for VTE Prophylaxis in Hospitalized Patients

Most hospitalized patients have at least one risk factor for venous thromboembolism (VTE), such as pulmonary embolism or deep venous thrombosis. The American College of Chest Physicians (ACCP) has released guidelines on VTE prophylaxis in hospitalized, nonsurgical patients, including those with acute stroke.

Recommendations

Patients should be assessed for the risk of thromboembolism and bleeding before the initiation of VTE prophylaxis.

The decision to initiate VTE prophylaxis should be based on the patient's individual risk of thromboembolism and bleeding, and the balance of benefits versus harms. Risk factors for thromboembolism are inherited (e.g., factor V Leiden mutation, prothrombin gene mutation, protein S or C deficiency, antithrombin deficiency) or are acquired (e.g., surgery, cancer, immobilization, trauma, presence of a central venous catheter, pregnancy, medication use, congestive heart failure, chronic renal disease, antiphospholipid antibody syndrome, obesity, smoking, older age, history of thromboembolism). Although there are many tools for assessing thromboembolism risk, there is insufficient evidence to recommend one over the others. General evidence regarding risk factors also may be used to make decisions about the need for prophylaxis.

Heparin or a related drug can increase the risk of bleeding, especially in older patients; women; patients with diabetes mellitus, hypertension, cancer, alcoholism, liver disease, severe chronic kidney disease, peptic ulcer disease, anaemia, poor treatment adherence, previous stroke or intracerebral haemorrhage, bleeding lesions, or bleeding disorder; and in patients taking certain concomitant medications. [4]

Prophylaxis with heparin or a related drug is recommended unless the risk of bleeding outweighs the likely benefits.

Prophylaxis with heparin has been shown to significantly reduce pulmonary embolisms in hospitalized patients, although bleeding events were increased. In most patients, the clinical benefit of decreased pulmonary embolisms outweighs the risk of bleeding. Evidence is insufficient to conclude that these risks and benefits differ in patients with stroke, although prevention of recurrent stroke may be an added benefit in these patients.

The optimal duration of heparin therapy is unclear. The benefits and risks are not significantly different between low-molecular-weight heparin and unfractionated heparin, and fondaparinux (Arixtra) has not been directly compared with heparin. The choice of medication should be based on ease of use, adverse effect profile, and cost. [4]

Mechanical prophylaxis with graduated compression stockings is not recommended.

Use of graduated compression stockings was not shown to be effective in preventing VTE or reducing mortality and can cause clinically important damage to the skin. Intermittent pneumatic compression may be a reasonable option if heparin is contraindicated, because evidence suggests that it is beneficial in patients undergoing surgery. However, the therapy has not been sufficiently evaluated as a stand-alone intervention in other patients. [4]

1.2About the American College of Chest Physicians

The American College of Chest Physicians is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. With more than 19,000 members representing 100+ countries around the world, their mission is to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research. This includes connecting health-care professionals to the latest clinical research and a wide array of evidence-based guidelines through the *CHEST* Journal, while also serving as a total education resource for clinicians. The first medical association with a clinical simulation program accredited by the Society for Simulation in Healthcare, the ACCP also provides hands-on training through innovative simulation education. The CHEST Foundation, the philanthropic arm, provides members with grants, patient education tools, and other resources to help their patients live and breathe easier.

Guideline Development

CHEST Guidelines are based on a rigorous methodology, striving to meet the highest standards in guideline development, as outlined by the National Academy of Medicine (NAM).

Guideline panels are carefully selected, screened for conflicts of interest, and include clinical experts who provide their expertise to the interpretation of the evidence and development of the recommendations. Because of the recognized need for credible clinical guidance in topic areas where there is no or weak supporting evidence for a formal guideline, the methodology accommodates to the complete evidence-continuum, from the highest level of supporting evidence (guidelines) to the lowest level of supporting evidence (consensus statements), with the hybrid approach in between using a combination of both processes.

Living Guidelines Model

CHEST currently implements a "Living Guidelines Model" in the creation of its clinical practice guidelines. A living guideline is a systematically developed, evidence-based, and continually updated series of recommendations for the diagnosis and management of medical conditions. Living guidelines are intended to inform both health-care providers and patients in making educated clinical decisions.

Guideline Methodology

Producing trustworthy clinical practice guidelines involves a rigorous evidence-based approach to identifying and synthesizing the literature that forms the evidence base for the guideline recommendations. The evidence that informs the recommendations is collected through a rigorous systematic review of key questions formulated through the PICO (Patient / Intervention / Comparator / Outcome) development process. All studies included in a body of evidence are assessed for their quality using the GRADE approach.

1.3 Need of the Study

Although venous thromboembolism (VTE) is the main preventable cause of death in hospitalised patients, VTE prophylaxis is still not routinely administered in most hospitals. There are numerous barriers to prophylaxis use, especially the natural resistance to change, fear of side effects, lack of effective institutional policies, and even lack of knowledge regarding the guidelines or difficulties in remembering the recommendations. Studies assessing the adequacy of VTE prophylaxis are usually limited to an analysis of the number of patients at risk and the number who received prophylaxis (mechanical or drug). In addition, patients not at risk for a VTE who received improper prophylaxis are not typically described in these studies.

2. AIMS AND OBJECTIVES

2.1 Aim

To analyze the use of drugs in prophylaxis of venous thromboembolism in a tertiary care hospital.

2.2 Objective

- To assess the proportion of patients receiving appropriate VTE prophylaxis (right drug, dose, frequency, and duration) after admission to general internal medicine units.
- To assess the adherence to guidelines.
- To describe reasons why VTE prophylaxis is inappropriate.

3. METHODOLOGY

***3.1Study Design*:** A prospective, observational study

3.2Study Duration: study was conducted for a duration of six month

3.3 Study Site:Study was carried out in Osmania General Hospital of the Telangana state (India), which is a 1100 bedded tertiary care hospital.

3.4Study Criteria:

Inclusion criteria
Either gender patients admitted to Medical Wards of OGH
Patients who are at risk of VTE with at least one predefined VTE risk factor.
Age >18 years

Exclusion Criteria
Refusal to be part of study
Pregnant women
Hospital stay less than 48 hrs.
Immobilization less than 24hrs
Patients who have coagulopathies.
Patients receiving Therapeutic Anticoagulation

3.5 Risk assessment model

Table 1 Modified PADUA Prediction Scale

Risk Factor	Points
Critically Ill	4
Inflammatory Bowel Disease	4
Active Cancer*	3
Previous VTE	3
Reduced Mobility**	3
Thrombophilic Condition***	3
Recent (< 1month) Trauma/Surgery	2
Age ≥ 70 years	1
Heart or Respiratory Failure	1
Acute Myocardial Infarction or Ischemic Stroke	1
Acute Infection or Rheumatologic Disorder	1
BMI ≥ 30	1
Ongoing Hormonal Treatment	1

Modified Padua Prediction Score (modified after Kucher) assigned points to the 11 common VTE risk factors and categorized hospitalized medical patients as low risk (< 4 points) or high risk (≥ 4 points) for VTE. Hence for baseline risk for low-, moderate and high-risk strata, we used risk estimates provided by the Padua Prediction Score. Despite the limitations of this risk model (small number of events, suboptimal validation), this model provides the best available basis for judging hospitalized patients' risk.

*[*Active cancer is defined as local or distant metastases and with chemotherapy or radiation in the previous 6 months **Reduced mobility is defined as anticipated bed rest with bathroom privileges for at least 3 days. ***Thrombophilic condition is defined as defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, or antiphospholipid syndrome]*

3.6 Plan of Study:

This study was approved by institutional review boards (IRB). Ethical approval was obtained from our local ethics committee. Patients fulfilling the study criteria were selected. This is a non-interventional, observational study; thus, no patient consent was required.

Data collection strategy consists of analyzing, by a group of Pharm D students, the medical charts of randomly selected patients in Osmania General Hospital. A clinical process audit will be taken from medical charts and, when necessary, nursing records. Data on risk factors for VTE and prescription of pharmacological and non-pharmacological thromboprophylaxis will be collected.

Data on risk factors for VTE and prescription of pharmacological and non-pharmacological thrombo-prophylaxis was collected on appropriate data collection form which had been designed and the following information were collected through it:

- Demographic data: sex, age
- Clinical data: history of present illness, past medical history, family history, medication history, and social history.
- From the obtained data associated risk factors for VTE and co-morbid conditions present in the patient were gathered. The risk associated are verified as per Modified Padua Prediction score.
- Patients are monitored for the medications given, ADRs and other drug interactions.
- Prophylactic therapy given is evaluated as per ACCP Guidelines and, if any, deviations were noted.

4. OBSERVATIONS AND RESULTS

4.1Prevalence of VTE risk factors in different genders

All clinical and surgical patients admitted into general medicine unit of the hospital during the study period were analyzed.Out of the 150 patients who were at risk of VTE, only 100 patients met our criteria and were included in the study. More prevalence was seen in the male patients, as shown in Figure 1, where 58% of the patients admitted were male and only 42% patients were female.

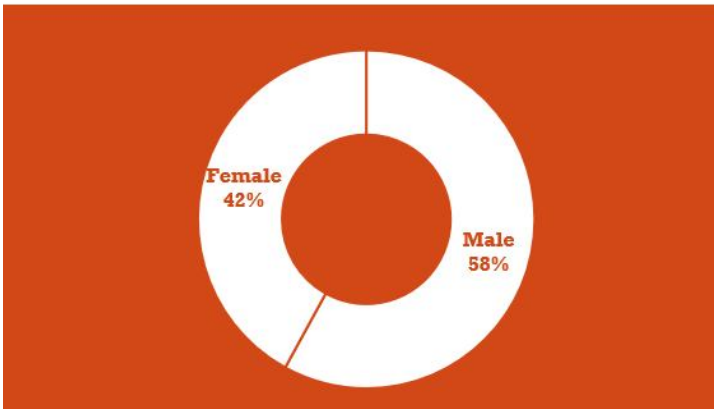

Figure 1 Prevalence of VTE risk factors in different genders

4.2Prevalence of VTE risk factors in age groups of different genders

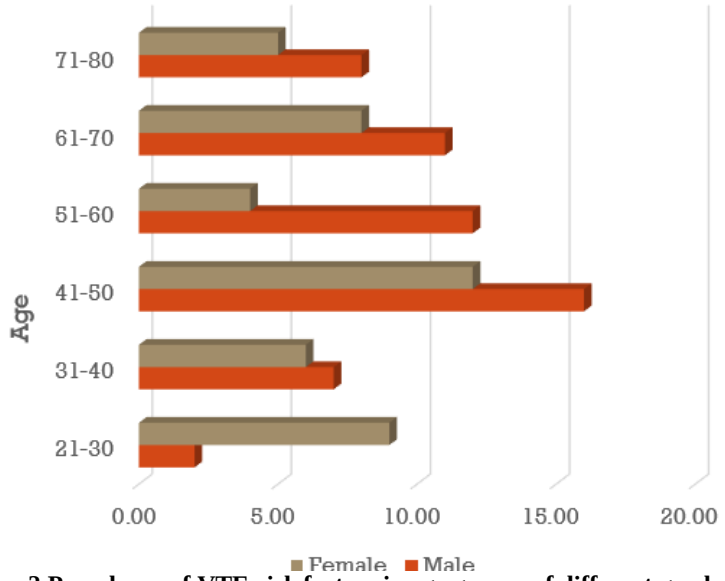

Figure 2 Prevalence of VTE risk factors in age groups of different genders

The age group with the highest number of cases observed was 41-50 years in both male and female gender. From Figure 2, we see that 27.5 % of the male patients and 28.5% of the female patients belonged to this age group.

4.3 Prevalence of VTE risk factors in surgical and non-surgical patients

Patients admitted in to the general medicine care unit of Osmania General Hospital were analyzed. Prevalence of VTE risk factors was seen more in the non-surgical patients than surgical patients. 69% of the patients belonged to the non-surgical group, while only 31% of the patients belonged to the surgical group. (Table 2)

Table 2 Prevalence of VTE risk factors in surgical and non-surgical patients

	Number of patients (n=100)
Non Surgical	69
Surgical	31

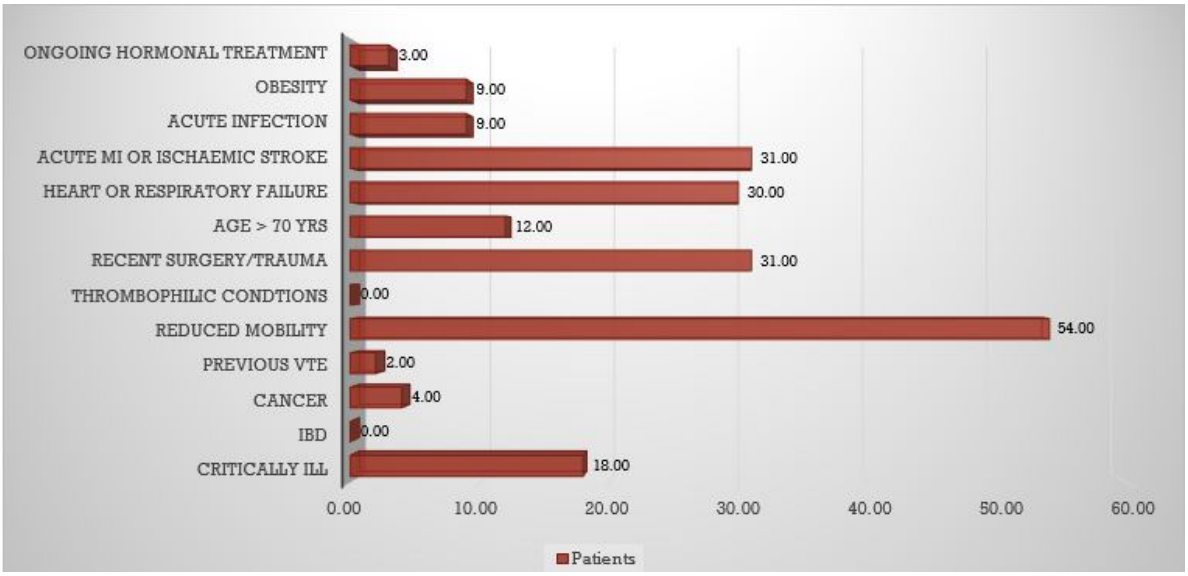

Figure 3 Distribution of Risk Factors

4.4 Distribution of risk factors

Based on the Modified PADUA Prediction Scale, distribution of the predefined VTE risk factors was observed. The most commonly observed risk factor was reduced mobility, with 54% of the patients in this category. Recent surgery and Stroke were the second most common factorobserved, each being observed in 31 patients. The other risk factors observed are shown in Figure 3.

4.5 Distribution of risk level

Based on the scores allotted to different risk factors in Modified PADUA Prediction Scale, the patients were classified as high, moderate and low risk. High and low risk levels were seen in equal number of patients (41%), while moderate level of risk was seen in only 18% of the sample size. (Figure4)

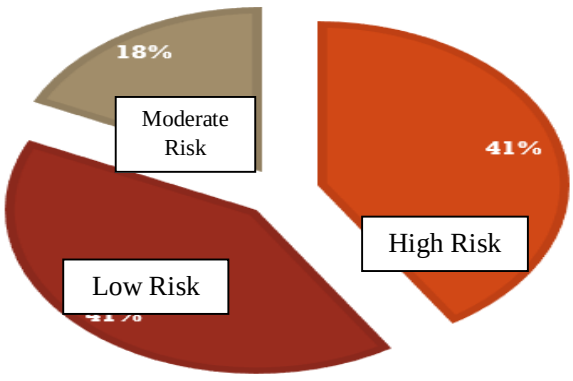

Figure 4 Distribution of Risk Levels

4.6 Distribution of patients based on prophylactic therapy

Figure 5 Distribution of patients based on prophylactic therapy

Out of the studied sample size of 100 patients, 65 patients were given VTE prophylactic therapy. The rest 35 patients were no given any therapy, both pharmacological and non-pharmacological (Figure 5).

4.7 Distribution of Patients Who are Receiving Therapy as per 9th ACCP Guidelines

Based on 9th ACCP Guidelines for Thromboprophylaxis patients were analyzed for appropriateness of their therapy. Out of the 35 patients that were not given any therapy at all, there were some who were at high risk VTE, and yet they were not given the prophylactic therapy. Also, out of 65 patients who received therapy, only a part of these patients was given appropriate therapy according to the guidelines. All the other patients, including the ones who needed the therapy but were not prescribed are classified under inappropriate therapy. Thus, it was found that 65% of the patients were given appropriate therapy and 35% were prescribed inappropriate therapy. (Figure 6)

Figure 6 Distribution of Patients Who are Receiving Therapy as per 9th ACCP Guidelines

4.8 Time taken to start the therapy

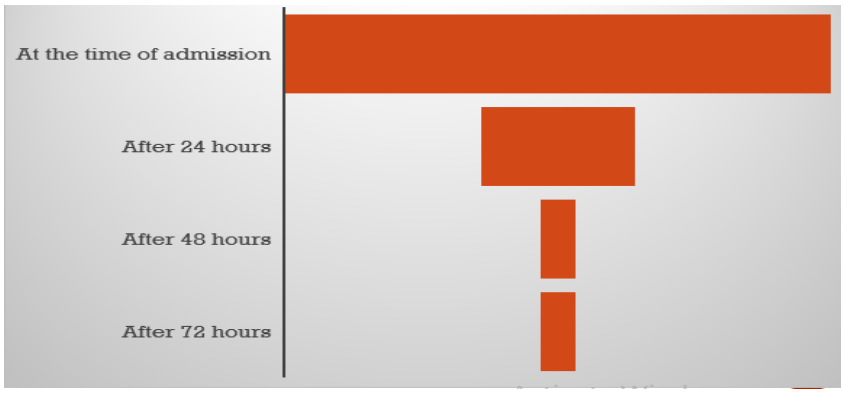

Figure 7 Time taken to start the therapy

Most of the patients started their therapy at the time of admission (Figure 7). While, for some patient's therapy was started 24 hours after admission in to the hospital (13%), 48 hours after admission (3%) and 72 hours after admission (3%).

4.9 Drugs used for prophylaxis

Therapy for VTE prophylaxis was composed of oral antiplatelets and oral or parenteral anticoagulants. Aspirin was the most commonly used drug, prescribed to 57% of the patients, followed by clopitab which was given to 24% of the patients. Other drugs used were heparin (17%), acitrom (5%) and enoxaparin (4%), as shown in Table 3. Out of the 65 patients who received therapy, 41 patients were given combination therapy. The most common combination used was aspirin+clopitab (59%). Other combinations of drugs prescribed were aspirin+heparin (29%), aspirin+enoxaparin (7%) and aspirin+acitrom (2%), depicted in Table 4.

Table 3 Drugs Used for Prophylaxis

Combinations Used	Number of times prescribed (n=41)
Aspirin and Clopidogrel	24
Aspirin and Heparin	12
Aspirin and Enoxaparin	3
Aspirin and Acitrom	2

Table 4 Combination of Drugs Used

	Number of Patients (n=65)
Aspirin	57
Heparin	17
Acitrom	5
Enoxaparin	4
Clopitab	24

5. DISCUSSIONS

This was prospective observational study with the primary objective, to evaluate the adequacy of VTE prophylaxis in a general medical ward and to present the results in a systematic manner, including the results of patients who were and were not at risk and details regarding why the use of prophylaxis was correct or incorrect.

Out of the 100 patients that were screened, men constituted for about 58% of the patients while 42% of the patients observed were females. The most common age group that was observed among the patients was 41- 50 years in both, male and female genders. The ages ranged from 18 years to 80 years. The observations were like findings of the study by Lee et al (2009), where men constituted 48% and women 52% of the group, with a mean age of 45 years [5]. Gender of the patient does not seem to have any special significance when considering the risk for VTE in hospitalized patients. Both the studies have demonstrated almost equal number of both male and female patients at risk of VTE.

However, one special feature of medical patients is their age; most of the medically ill patients are adults with age more than 40 years. Risk of thrombosis increases sharply with age; from approximately 1 in 10,000 people per year for those younger than 40 years to 1 in 100 people per year for those 75 years and older. Thus, as the average population age increases in any community, the prevalence of VTE increases too.

In a multiple logistic regression analysis, Alikhan *et al (2004)*, showed that age older than 75 years, cancer, previous VTE, acute infectious disease and chronic respiratory disease were all independent risk factors for VTE. Previous VTE had the highest odds ratio [OR: 2.06; 95% confidence interval (CI): 1.10–3.69]. Other significant risk factors for VTE in medical patients include confinement to a hospital or nursing home, extremity paresis, central venous catheterization

and heart failure. In females, additional risk factors include hormonal therapy with oral contraceptive pills, hormone replacement therapy, and selective estrogen receptor modulators like Tamoxifen and Raloxifene. Diseases like myeloproliferative disorders, especially essential thrombocythemia, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, Bahçet syndrome and inflammatory bowel disease, are some of other medical illnesses associated with higher risk of VTE. [6]

The most commonly observed risk factors observed in the current study was reduced mobility, 54% of the sample size presented with this condition. Other risk factors which were repeated in most patients was surgery (31%), acute MI or stroke (31%) and heart or respiratory failure (30%). This contrasted with the study carried out by Lee et al (2009), malignancy (31%) was the most common predisposing factor, followed by postoperative status (30%). The incidence following surgery was five per 10 000 operations. General surgery patients had the highest incidence of deep vein thrombosis (DVT; 40.3%), while the incidence in orthopedic patients was 20.1%. [5]

Incidence of risk factors in surgical patients was only 31% in this study. This was significantly higher than the results obtained in the study carried out by Khalafallah et al (2016), where on 13% of the patients observed had a history of surgery in the past one month. Other risk factors that were observed in our study but were not statistically significant are critical illness (18%), obesity (9%), acute infection (9%) and cancer (4%). [7]

The Modified PADUA Prediction Scale was used in this study to classify patients as high, moderate and low risk levels. Equal number of incidences were seen of high and low risk patients (41%), while moderate risk level patients were significantly lesser (18%). Deheinzelin et al conducted a similar study in Brazil, using Caprini Score, and found that 81% of the patients were at high risk for VTE, while lesser incidences were seen of low (10%) and moderate (10%) risk patients. [8]

Out of the 100 patient charts examined (patients who received therapy and other who did receive any kind of therapy), when analyzed for appropriateness based on the 9th ACCP guidelines, it was found that only 65% of the patients received appropriate therapy while the rest 35% of the patients were prescribed inappropriate therapy. The most common reasons of inappropriate therapy were found to be prescribing aspirin as monotherapy and not giving prophylactic therapy to high risk patients. In contrast, in the study carried out by Mejilla et al (2017), where 79.6% of the patients at risk of VTE received appropriate prophylaxis. The 2 most frequent reasons for deeming VTE prophylaxis to be inappropriate were not providing a mechanical method of VTE prophylaxis for patients with a bleeding contraindication and wrong dose of pharmacologic prophylaxis [9]. While, observations like the current study were seen in the study carried out by Yeramilli et al (2016), where

70% patients received appropriate therapy [10]. The small difference may be due to different sample sizes of the studies.

In the hospital, where this study was conducted employed antiplatelets and anticoagulants for VTE prophylactic therapy, while no mechanical methods were utilized. The most commonly used drug was Aspirin, prescribed in 87.6% of the cases. This was followed by Clopitab prescribed to 36.9% of the patients. Other drugs that were used for prophylaxis of VTE were Heparin (26.15%), Enoxaparin (6.1%) and a LMWH, Acitrom (7.6%). The most commonly used combination of drug was Aspirin and Clopitab. In this study we observed the use of antiplatelets more than anticoagulants. This contrasted with the study carried out by Lee et al (2009), where ninety-eight percent of the patients with VTE were managed by anticoagulation alone, consisting of both unfractionated heparin (UFH) as well as LMWH. During the initial part of the study, UFH alone was used. The latter part of the study saw increasing use of LMWH for the treatment of VTE. [5]

6. CONCLUSION

The results of this study provide insight into current prescribing patterns for VTE prophylaxis within the medicine unit of study institution. Although these results reflect lower-than-desired rate of appropriate VTE prophylaxis therapies, variations in definitions and data collection may have contributed to the discrepancy.

Despite its proven efficacy, VTE prophylaxis is clearly underutilized. Many reasons can explain this consistent underutilization. Lack of physician awareness and agreements on published VTE prophylaxis guidelines and the underestimation of the risks in this group of patients continue to be important barriers. However, lack of a validated VTE risk assessment model able to group medical patients into different risk categories is probably the most import barrier.

Appropriate VTE risk assessment strategies and adherence to guidelines for prophylaxis therapy are the two important steps that must be taken to improve the prescribing patterns of VTE prophylaxis. Morbidity and mortality from VTE are a significant problem in India. Correct DVT prophylaxis would reduce the incidence of VTE in India and bring down the mortality rates.

Further research is needed to determine how to promote the use of guideline concordant prophylactic therapy for VTE at-risk hospitalized patients.

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