Assessment of the Heparin and Enoxaparin Prophylaxis Protocol in Patients Receiving Care at Sina Hospital in Tabriz

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Abstract- Venous thromboembolism (VTE) poses a significant risk to hospitalized patients, accounting for approximately 10% of morbidity cases among this population. However, preventive measures such as heparin and low molecular weight heparin (LMWH), along with mechanical interventions like graduated compression stockings (GCS), can effectively mitigate this risk. The aim of this study was to investigate the rational use of DVT prophylaxis regimen in hospitalized patients. A prospective and descriptive study was conducted randomly in various wards of the hospital throughout 2017. 335 participants were randomly assessed using an already designed questionnaire containing demographic information (age, weight, height, etc.), medical history, type of prophylaxis administered, laboratory tests, prescribed medications, the Geneva score for thrombosis risk evaluation (low risk: 0-2, high risk: ≥3), and bleeding risk assessment tool (low risk: 0-7, high risk: ≥7). Randomly, the medical records of 335 patients admitted to Sina Hospital and who received VTE prophylaxis with heparin (87.8%), enoxaparin (12.54%), and GCS (1.79%), were carefully reviewed over a period of 12 months. According to the guidelines, only 235 patients (70.1%) required anticoagulant prophylaxis, while the remaining 100 patients (29.8%) were not eligible for such prophylaxis. Additionally, out of the 335 patients studied, only 6 received GCS, although only one patient actually necessitated this intervention. Consequently, the total cost of inappropriate anticoagulant prophylaxis was estimated to be 68,270,500 Rials. The appropriate utilization rate of VTE prophylaxis was 70.1%, with heparin being the most commonly prescribed medication. Further, the study highlights the cost implications of inappropriate prescription practices. To address these issues, educational programs and the implementation of clinical practice guidelines within general Hospitals are highly recommended.

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Introduction

VTE (venous thromboembolism), which includes DVT (deep vein thrombosis) and PTE (pulmonary thromboembolism), poses a significant public health concern and causes substantial morbidity among hospitalized patients. VTE can be categorized as provoked or unprovoked based on the presence of identifiable risk factors. Provoked VTE occurs when it is caused by major transient risk factors such as surgery, trauma, immobility, or persistent risk factors like cancer. (1,2). On the other hand, unprovoked VTE refers to cases

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where no identifiable cause(s) are found. This categorization is important in determining the duration of anticoagulant therapy since the risk of recurrence is higher in unprovoked VTE compared to VTE provoked by major transient risk factors. The principal prophylactic measures for both provoked and unprovoked VTE include the use of pharmacologic options such as blood thinning medications (anticoagulants) or non-pharmacologic preventive methods like leg elevation, early ambulation, or compression stockings (3,4). In Iran, the two most commonly used anticoagulants in hospitalized patients are unfractionated heparin and low molecular weight heparins, particularly enoxaparin. One of the most serious complications of DVT is pulmonary embolism, which occurs when a blood clot from the veins travels to the lungs. The presentation of pulmonary embolism can vary from asymptomatic cases to symptoms such as shortness of breath, chest pain, right ventricular dysfunction leading to arrhythmia, and even sudden death (5). The three main factors responsible for the formation of blood clots in blood vessels, known as Virchow's triad, are blood flow stasis, hypercoagulability (increased tendency for blood to clot), and endothelial injury (6). While many patients with DVT may not experience any symptoms, some common signs and symptoms include pain, heaviness, cramps, and persistent swelling in the affected extremity. These symptoms may worsen with exercise and improve with rest. Post-thrombotic syndrome, a complication of DVT, can present with cutaneous manifestations such as telangiectasia (dilated small blood vessels), skin hyperpigmentation, ulceration, and rarely a severe condition called Phlegmasia cerulean dolens (7,8). The costs associated with DVT treatment in hospitals are generally high (9), reflecting the significant resources required for diagnosis, management, and prevention of complications. Thromboprophylaxis, which involves measures to prevent blood clot formation, reduces the risk of VTE in both medical and surgical patients. Studies have shown that thromboprophylaxis is more effective in reducing mortality in surgical patients compared to medical patients. The exact reasons behind this difference are unclear but may be related to the higher prevalence of comorbidities in medical patients (10). DVT is a common complication that can occur following fractures in the lower limbs, particularly among the elderly population and individuals with limited mobility.[10] If a blood clot caused by DVT travels to the lungs, it can result in PE (11). Although there has been a decrease in the occurrence of severe cases of PE and hospital mortality, the overall number of admissions for PE has actually increased from 60,000 in 1993 to over 202,000 in 2012. However, this rise in admissions is primarily attributed to advancements in diagnostic techniques rather than a true change in the underlying epidemiology (12). Enoxaparin offers several advantages over heparin, including (a) predictable consequences: the effects of enoxaparin treatment are more predictable compared to heparin; (b) longer half-life and lower bleeding risk: enoxaparin has a longer half-life and a lower risk of bleeding when compared to heparin. These make it a safer option for patients; (13) (c) lower risk of thrombocytopenia: enoxaparin carries a lower risk of thrombocytopenia, which is a condition characterized by a decrease in platelet count, often caused by immune reactions to heparin; (d) reduced risk of osteoporosis: enoxaparin is associated with a lower incidence of osteoporosis compared to heparin. This is an important consideration for long-term users; (e) no activated partial thromboplastin time (aPTT) monitoring required: unlike heparin, enoxaparin treatment does not require regular monitoring of the aPTT. This simplifies the administration process; (f) no dose adjustment based on aPTT: enoxaparin does not require dose adjustment based on aPTT levels, further streamlining the treatment process; (14) (g) cost-effectiveness: both the treatment and prophylaxis with enoxaparin are considered more cost-effective compared to the expenses associated with treating heparin-induced thrombocytopenia (9). In addition to pharmacological thromboprophylaxis, there are mechanical treatment options available, such as intermittent pneumatic compression (IPC) and GCS. IPC is particularly beneficial for surgical patients who may have limited mobility during their hospital stay. On the other hand, GCS is more convenient for extended use in outpatient settings (15). The efficacy of mechanical prophylaxis remains controversial. While some studies suggest a reduction in DVT and PE in surgical patients who use mechanical methods, others argue that pharmacological thromboprophylaxis is sufficient for moderate to high-risk surgical patients. (16,17). Furthermore, VTE is a common complication of malignancies. While VTE may be detected after the diagnosis of malignancy in many cases, it can also be discovered during treatment or diagnostic procedures. It's important to note that although VTE prevalence is high in malignancies, not all individuals with malignancies will experience VTE (17).

Materials and Methods

To provide strict quality assurance with regard to

ethical issues, the original study protocol was implemented based on the concepts of ethics in biomedical research that originated from the Declaration of Helsinki. This is a prospective and descriptive study, conducted at Sina Hospital of Tabriz University of Medical Sciences over a 12-month period. It has 27 clinical wards and 8 ICU wards and has 301 active beds. We aimed to evaluate the appropriate use of prophylactic anticoagulants and mechanical modality for patients in surgical and internal wards. It should be noted that informed consent has been obtained from all patients participating in the study. The target population included all patients admitted to Sina Hospital and subjected to anticoagulant prophylaxis**.** A final sample of 335 patients was randomly selected by using a simple computer-generated random number (simple randomization) for study initiation and data collection. To collect data, a questionnaire was utilized, which encompassed demographic information (such as age, weight, and height), medical history, information regarding the type of prophylaxis received, laboratory test results, prescribed medications, and checklists for assessing thrombosis risk based on the Geneva score (0-2 indicating low risk, three or higher indicating high risk) and bleeding risk (0-7 indicating low risk, seven or higher indicating high risk). Additionally, records of the total consumption and costs of anticoagulant and mechanical prophylaxis were obtained from the hospital pharmacy. Inclusion criteria for the study encompassed all patients admitted to the hospital who received VTE prophylaxis. On the other hand, the following exclusion criteria were also employed: definitive or probable diagnosis of PE or DVT, hospitalization duration less than 24 hours, and active bleeding, brain hemorrhagic stroke, or any contraindication for anticoagulant/mechanical prophylaxis for DVT. Patients in surgical wards were evaluated using the Caprini risk score checklist (18), while patients in internal wards were assessed using the Geneva risk score checklist (19) Furthermore, all patients also underwent evaluation using the bleeding risk factor table (20). Additionally, antithrombotic therapy for VTE Disease, 2016 CHEST guideline was used for the assessment of an appropriate anticoagulant prophylaxis regimen.

The collected data were analyzed descriptively using SPSS software version 20. Data were reported as mean±SD or as number (%).

Results

During a 12-month period, 335 patients receiving VTE prophylaxis were randomly included. The patients were 151 females with a mean age of 62.1±18 and 184 males with a mean age of 57.4±18.1. The mean weight of females was 71.4±12.9 kg and males 68±18.1 kg. The body mass index (BMI) of female and male patients was 26.7 and 24.7, respectively. Out of 335 participants in this study, 48(14.3%) had a bleeding risk. 235 of the total patients (70.1%) were indicated to receive anticoagulants, of which 202 (86%) were prescribed heparin and 33 (14%) received enoxaparin. On the other hand, out of 100 (29.8%) patients who were not candidates for anticoagulant administration, 91 patients (91%) received heparin and 9 (9%) enoxaparin.

Table 1 shows that out of the total of 335 participants in this research, 48 (14.3%) were at risk of bleeding. 235 (70.1%) of the patients were indicated to receive anticoagulants, of which 203 received heparin and 32 people (14%) also received enoxaparin. Out of a total of 100 (29.8%) patients who did not have an indication for anticoagulants, 91 (91%) received heparin and 9 (9%) received enoxaparin.

Table 1. Appropriateness of DVT prophylaxis modalities

Patients	Number(%)
Patients who had bleeding risk factors (percentage)	48 (14/%3)
Patients who were indicated to receive anticoagulants	235 (70/%1)
Patients who had indications for anticoagulants and received heparin (percentage of total indications for anticoagulants)	203 (86/%3)
Patients who had indications for anticoagulants and received enoxaparin (percentage of total indications for anticoagulants)	32 (%14)
Patients who did not have an indication for receiving anticoagulants	100 (29/%8)
Patients who did not have an indication for receiving anticoagulants but received heparin (percentage of the total number of patients with no indication for receiving anticoagulants)	91 (%91)
Patients who did not have an indication for receiving anticoagulants, but received enoxaparin (percentage of the total number of patients with no indications for receiving anticoagulants)	9 (%9)
Patients who received GCS	6 (1/%7)

Prophylaxis agent usage

Heparin was the most commonly prescribed agent for

prophylaxis, with a cost of 54,406,500 Rials.

Cost analysis

The total cost is provided in Table 2, which shows that the total cost of anticoagulant consumption was equal to 454,420,000 rials.

The irrational consumption costs of anticoagulants are presented in Table 3, where enoxaparin has a greater share than heparin in irrational consumption.

The cost of anticoagulants used for patients with a high risk of bleeding was 82.958.500 Rials for patients who took heparin and 5.372.000 Rials for patients who took enoxaparin, which shows that heparin has a higher cost.

Lastly, Finally, according to the data obtained from this study, which compared the percentage of patients with a high risk of bleeding to the total number of patients who were indicated for anticoagulant prophylaxis, the results are that the percentage of patients with a high risk of bleeding compared to The percentage of patients receiving heparin was 21.16% and the percentage of patients with high bleeding risk compared to all patients receiving enoxaparin was 9.28%. Accordingly, more patients received heparin.

Table 2. Total costs

Costs	Price per ampule (Rial)	Number	Total (Rial)
Total heparin costs	41,500	9448	392,092,000
Total enoxaparin costs	15,8000	366	57,828,000
Total GCS costs	750,000	6	4,500,000
Total VTE Prophylaxis costs		454,420,000	

GCS (graduated compression stockings), VTE (Venous thromboembolism)

Table 3. Percentage of inappropriate DVT prophylaxis administration.

Modalities	Percentage
Heparin	13.87 %
Enoxaparin	22.67 %
Compression socks	16.67 %

Discussion

In our study, the data revealed interesting insights regarding anticoagulant and GCS prescriptions for PE and DVT prophylaxis. Out of all the prescribed anticoagulants, 87.76% were heparin, 12.54% were enoxaparin, and a small percentage of 1.79% consisted of GCS. When analyzing the distribution of 147 DVT prophylaxis, it was found that it was more commonly prescribed to men, accounting for 54.93% of cases, compared to women at 45.07%. However, the role of sex as a risk factor for VTE remains inconsistent across different studies. Some research studies have indicated higher VTE prevalence in men (21), while others have suggested an increased risk among females (22,23). The incidence rate of VTE can also vary depending on age and the location of the thrombosis. For instance, one study conducted by REJ Roach et al. highlighted that younger women had a higher likelihood of developing VTE due to reproductive risk factors. Additionally, S Barco et al. reported a greater prevalence of isolated distal DVT among young women. Conversely, in middle age, the incidence of VTE, particularly proximal DVT, was higher in men (24,25). The study conducted involved 335 patients who were administered heparin, enoxaparin, and GCS as prophylaxis. Out of these patients, only 235 actually required prophylaxis according to the guidelines. Among the 235 patients, 86% received heparin while only 14% received enoxaparin. The study found that the overall appropriateness of prophylactic anticoagulation was 70.1%. Another study conducted at a different hospital in Tabriz by Ali Akbari A *et al*., focused on 300 patients admitted to internal and surgical wards (26). The results revealed that the compliance rate for pharmacological prophylaxis using heparin and enoxaparin was lower in the internal wards at 56.6%, but relatively higher in surgical wards at 77.3%.

Additionally, a study by Ms. Laleh Mahmoodi *et al*., investigated the adherence to guidelines for heparin 165 and enoxaparin usage patterns in thromboembolic prophylaxis (27). Out of 305 patients, 83.3% received prophylactic treatment in accordance with the guidelines. Of the total patients, 61.6% were classified as moderate to high risk and required prophylaxis, among whom 93%

received the correct prophylactic treatment. The study reported adherence rates of 77% for heparin and 95.7% for enoxaparin. When comparing these findings with Ms. Laleh Mahmoodi's study, it is observed that there is no significant difference in terms of heparin prophylaxis (77% in Ms. Laleh Mahmoodi's study and 86.38% in our study) (27,28). However, a notable disparity exists in the administration of enoxaparin prophylaxis (95% in Ms. Laleh Mahmoodi's study and 14.04% in this study). These results suggest variations in adherence to thromboembolic prophylaxis guidelines across different studies and hospitals, particularly with respect to the use of enoxaparin. Further investigations are needed to understand the underlying reasons for these discrepancies and to enhance compliance with guidelines in clinical practice. The mentioned study calculated the wasted cost of heparin and enoxaparin forfara thromboembolic prevention and treatment. However, our study focused solely on VTE prophylaxis. Additionally, apart from heparin and enoxaparin, mechanical prophylaxis methods such as GCS have been examined, and the wasted cost for each approach has been calculated separately. Furthermore, our study analyzed the loss of anticoagulant expenses in patients at high risk of bleeding. The disparity in enoxaparin results can be attributed to the fact that a majority of our patients were hospitalized in internal wards and had underlying kidney diseases. Enoxaparin is not FDA-approved for use in dialysis patients due to reported severe bleeding issues associated with its use in dialysis and severe renal insufficiencies. Enoxaparin is primarily indicated for patients with clotting risks who have specific diseases or undergo certain surgeries. In our study, the number of patients eligible for enoxaparin prescription was lower than in the aforementioned study, which explains the discrepancy in enoxaparin consumption percentages compared to our study. In a study conducted by Syed Sikandar Shah *et al.*, (29), which evaluated appropriate thromboprophylaxis therapy in patients admitted to the general wards of two tertiary university hospitals in Cyprus, a total of 180 patients were examined. Enoxaparin was the most commonly utilized VTE prophylaxis in that study (58.8%), whereas our study only had a 12.54% prescription rate for enoxaparin. When considering the appropriateness of thromboprophylaxis, the percentage of patients receiving appropriate and inappropriate therapy was quite similar at 52.3% and 194 47.7 %, respectively (27). In our study, which included 335 patients, only 42 received enoxaparin. Among them, 33 (78.57%) were deemed appropriate candidates for enoxaparin treatment according to guidelines, while nine patients (43.21%) received it despite not meeting the criteria.

A prospective study conducted by Fanak Fahimi examined the appropriate usage of enoxaparin in patients admitted to Masih Daneshvari Hospital in Tehran (30). The findings indicated that 70.92% of the 200 patients received enoxaparin appropriately, while 28.70% received it inappropriately. Among those who received enoxaparin inappropriately, 53.47% were due to incorrect prescribed doses, and 75.51% were attributed to incorrect treatment duration or prophylaxis (30). In comparison to Fanak Fahimi's study, our study evaluated not only enoxaparin but also heparin and GCS for admitted patients. When comparing the results of the two studies, there is a similarity in the appropriate prescription of enoxaparin (92.70% in the mentioned study vs. 78.57% in our study) and a similarity in inappropriate usage (28.70% in the mentioned study vs. 21.43% in our study). The investigation of creatinine clearance in Fanak Fahimi's study revealed that eight patients (5.44%) had Clcr <30 ml/min (30). However, our study displayed higher numbers, with 63 patients (18.83%) having Clcr <30 ml/min. This indicates a higher percentage of patients with renal disease in our study received enoxaparin in spite of relative contraindication. Additionally, in Fanak Fahimi *et al*.'s study, evaluation of bleeding risk factors demonstrated that eight patients (5.44%) experienced bleeding. Out of these, 2 had epistaxis, 3 had bloody sputum, 1 had blood in stool, and 2 cases remained unidentified. In contrast, our study identified a risk of bleeding in 48 patients (14.33%), but no actual bleeding symptoms were observed (30). In 2018, Hirry Menon conducted a retrospective study comparing the costs associated with HIT caused by enoxaparin, used for both prophylaxis and treatment, to those of heparin (9). While Menon's study focused on calculating the wasted cost of heparin and enoxaparin for thromboembolic prevention and treatment, our study specifically examined the prophylactic aspect. Additionally, we expanded our investigation to include mechanical prophylaxis methods such as GCS and separately assessed the wastage cost associated with each method. Moreover, our study analyzed the cost loss related to anticoagulant usage in patients at a high risk of bleeding. However, it is worth noting that Menon's study revealed enoxaparin to be significantly more cost-effective than IV heparin when used for therapeutic anticoagulation but not for prophylaxis. When comparing the results of these two studies, it becomes apparent that our study incurred additional costs for patients and resulted in greater wastage of anticoagulants. Regarding the study by G.G. Alexander Trupie *et al*., in 2019, it evaluated the

prevention of DVT in patients undergoing neurosurgery (31). Despite the fact that the non-English language text of the study was not available, we made the comparison based on the results mentioned in the abstract. In this study, a random selection of neurological patients was divided into three groups. The first group received compression socks as treatment. The second group received intermittent pneumatic compression (IPC) in addition to GCS for the prevention of DVT. The third group served as the control group. In the first group, the treatment duration was 14 days or less, or until the patients were discharged from the hospital earlier if it happened before the 14-day mark. Among the 80 patients in this group, seven individuals (8.8%) developed DVT. The second group underwent treatment within 7 days, and out of the 78 patients in this group, seven individuals (9%) developed DVT. In the control group, consisting of 81 patients, 16 individuals (19.8%) were diagnosed with DVT. The results showed a noticeable difference between the experimental groups (compression socks alone or in combination with IPC) and the control group, suggesting that these interventions are effective in preventing DVT in neurological patients. A study by Mr. O. Agu *et al*., conducted in 2002, investigated the effects of compression stockings for the prevention of VTE. It demonstrated that this method effectively increases blood flow, reduces vasodilation, and improves venous wall function. In the aforementioned study, 15 patients who used only GCS were randomly examined. This prophylactic measure resulted in a 64% reduction in DVT risk in surgery patients and a 57% reduction in patients undergoing hip replacement (32). The effects of compression stockings are enhanced when combined with medications like heparin, making them recommended for high-risk DVT patients. However, it's important to note that Mr. O. Agu's study evaluated the effect of GCS solely in patients admitted to surgical units. In our study, patients from all wards were investigated, with 6 out of 335 patients receiving GCS in combination with heparin for DVT prevention. As mentioned in Mr. O. Agu's study, the combination of mechanical and pharmacotherapy yields better prophylaxis. According to a review article conducted by B. Tamowicz *et al*., in 2019, mechanical VTE prophylaxis utilizing GCS and IPC is recommended either following pharmacological prophylaxis or simultaneously in patients at high risk of bleeding. This study also emphasizes that the use of potential thromboprophylaxis methods alone is not sufficient and calls for increased education, focusing on the effectiveness of mechanical prophylaxis as a method with no bleeding risk (33). Dr. Mehran Kouchak conducted a study in 2011 to evaluate venous thromboembolism in the intensive care unit (ICU) of a teaching hospital in Tehran (34). This cross-sectional study examined patients admitted to the ICU of Imam Hossein Hospital over a one-year period. The patients' age, sex, underlying diseases, and treatments were recorded. Thromboembolism diagnoses were made based on clinical suspicion and confirmed through Doppler ultrasound. High-risk patients were identified using Wells' criteria and received prophylactic measures. In our study, we assessed patients across all wards of the hospital, recording their age, sex, underlying diseases, and treatments similar to the above-mentioned study. High-risk patients in the surgical unit were determined using Caprini criteria, while those in the internal ward were evaluated according to Geneva criteria. The results of our study also indicated that prophylaxis incurred high costs for patients and led to medication waste. Additionally, Dr. Mehran Kouchak's study demonstrated that age is an important factor in the development of VTE, with most diagnosed patients being over the age of 40 (35,36).

In this study, an attempt was made to check the level of adherence to the guidelines during the hospitalization of patients. And setting guidelines for a better and more accurate examination of the use of anticoagulants in the internal and surgical departments of Sinai Hospital. It would be better if the study were conducted in a larger population and with a greater variety of sectors and multicenter. The study should be conducted in an interventional way, and the rational use protocol of VTE prophylaxis should be implemented by all departments. The role of other anticoagulants in the prevention of VTE should also be examined.

These results suggest that a significant proportion of patients received appropriate DVT prophylaxis based on established guidelines. Heparin, a commonly used anticoagulant, was preferred in the majority of cases. However, it is concerning that there were instances of irrational prescriptions, leading to financial implications. It's important to note that further well-designed studies would be necessary to gain a more comprehensive understanding of the findings. All physicians and nurses are the target population for educational programs regarding the appropriate use of anticoagulant prophylaxis.

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