Heparin, Enoxaparin, and Mechanical Prophylaxis Utilization Evaluation in DVT Prophylaxis in a Major Teaching Hospital in West of Iran

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Background: Considering the high prevalence and risk of Deep Vein Thrombosis (DVT) and pulmonary thromboembolism (PTE) in hospitalized patients and the existence of different prophylaxis methods in these patients, the necessity of evaluating the rational administration of heparin or enoxaparin and mechanical prophylaxis is one of the important priorities. The present study aimed to evaluate the consistency of the Heparin/Enoxaparin administration in comparison to guidelines in patients admitted to Imam Reza Hospital.

Methods: In this prospective study drug use evaluation (DUE), 300 hospitalized patients receiving venous thrombosis prophylaxis were enrolled, of which 150 patients were selected from surgical wards and 150 patients from internal wards. The demographic and clinical data of patients were collected using clinical records of them. We used the checklists based on the Geneva System for patients admitted to internal wards and the Caprini Questionnaire for patients in surgical wards to evaluate whether patients had received heparin/enoxaparin prophylaxis and mechanical DVT prevention according to guidelines.

Results: In the surgical ward, prophylactic treatment for venous thrombosis was administered in 85 (56.6%) patients admitted to surgical wards in accordance with the clinical guideline and in the internal ward, in 42 (28%) patients, with a significant difference between two sections (P: 0.0001). Mechanical prophylaxis, including compressive socks, was performed in 99 (66%) patients in the surgical ward and in the internal ward only in 56 (37.4%) patients, according to the guideline. Drug prophylaxis was administered in surgical wards in 116 (77.3%) patients and in internal wards, in 79 (52.6%) patients according to the guideline.

Conclusion: Intravenous thrombosis prophylaxis, according to the guidelines, is more common in patients admitted to surgical wards than in internal wards. But in both sectors, statistics are far from international standards.

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Introduction
Venous thromboembolism includes DVT (deep vein thrombosis) and PE (pulmonary embolism), which have significant complications and mortality in hospitalized patients. Unprovoked VTE is when a specific cause and background are not found, and this indicates the influence of environmental factors and vice versa. Provoked VTE is when we have a specific background and risk factor, such as malignancy or immobility. The main prophylaxis of VTE is anticoagulants that the duration of prophylaxis treatment varies from 3 to 6 months depending on the underlying disease and risk factors (1).
Thromboprophylaxis reduces the risk of VTE in patients. While most studies show that thromboprophylaxis reduces the risk of death in surgical patients, the reason for this difference between surgical and internal patients is not known but is probably due to the high incidence of comorbidities in internal patients (2).

Despite significant medical advances in the prevention and treatment of DVT and PE, it is the most common preventable cause of death in a hospital, which in the United States is responsible for the deaths of about 150,000 to 200,000 people per year. It is estimated that more than half of internal patients are at risk of developing thromboembolism (2, 3).

Most studies in this area have examined the risk of VTE in patients who have not received anticoagulant prophylaxis, so it appears to be overestimated in 10 to 80% of studies (2).

According to published statistics, 11000 people in the United States are exposed to various complications related to the formation of thrombus or clots in deep veins and venous thromboembolism (4). For the first time in 1845, Virshu identified three major factors influencing deep vein thrombosis in the form of impaired blood flow (Due to lack of proper venous pumping resulting from impaired muscle contraction), vascular damage (due to activation of vasoactive amines or attributable to external layers on the organs) and increased coagulation (due to stimulation of thrombogenic factors following injury, including increased platelet aggregation and adhesion) (5). Given that venous thrombosis can lead to dangerous and occasionally fatal complications, its prevention is very important, especially in hospitalized patients who are at risk for major risk factors for venous thrombosis. Thus, Francis and colleagues, in a study of hospitalized patients with cancer, stated that these patients are at high risk for venous thrombosis; therefore, in the absence of active bleeding or high risk of bleeding, prophylactic administration of anticoagulants is unavoidable (6). So, in recent years, various mechanical and pharmacological treatments have been used in hospitalized patients to prevent venous thrombosis; these include unfractionated heparin and low molecular weight heparin.

Based on studies, mechanical prevention methods such as mechanical pressure are relatively ineffective, and they are not effective alone (7). Therefore, further research on increasing the effectiveness and reducing the side effects of prophylactic use of anticoagulants as a more effective treatment than mechanical methods is a topic of discussion among researchers and physicians (8). However, despite the introduction of guidelines and systems for calculating the risk of venous thrombosis in patients, the use of these cases has not become common among physicians, and in some cases, not following these guidelines not only endangers the lives of patients but can also lead to a loss of costs and drug reserves following the improper administration of anticoagulants (9, 10). In a systematic review by Motte et al., the researchers concluded that although different risk assessment models and numerous treatment recommendations are available for the prevention of venous thrombosis, the best decision for treatment and prevention in patients should be based on a combination of clinical guidelines and patients’ clinical findings. In this case, a balance can be struck between the risk of venous thrombosis and the risk of bleeding (11).

Due to the high prevalence and risk of DVT and PTE in hospitalized patients and also the existence of different prophylaxis methods in these patients, the need to evaluate the rational use of prophylaxis with heparin or enoxaparin is one of the important priorities in terms of reducing costs and rationalizing prophylaxis. It gets more important when these drugs are among the most expensive drugs in the hospital due to high consumption, so the aim of this study was to investigate the rational use of heparin/enoxaparin and mechanical prophylaxis for thromboembolic events in DVT prophylaxis regimens in patients admitted to Imam Reza Hospital during eight months.

Methods
The present prospective drug use evaluation (DUE) study was conducted between April 2018 and October 2018 in Imam Reza Hospital (the largest teaching hospital in the northwest of Iran), affiliated to Tabriz University of Medical Sciences, Tabriz, Iran.

This study was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences ID: TBZMED. REC.1397.659. Because there was no need for intervention or aggressive procedure on the patient, there was no need for moral consent. However, in order to obtain information about patients’ files, the necessary coordination was done with the head of the hospital and wards, while maintaining the confidentiality of patients’ information.

Consented patients who were admitted to Imam Reza Hospital between the study period and received heparin, enoxaparin, or mechanical prophylaxis for thromboembolic events were included in the present study. Patients who received treatment regimen for thromboembolic events were excluded.

During the study period the demographic and clinical data of patients including age, sex, the risk of thrombosis, bleeding and the pattern of anticoagulant therapy, whether mechanical or pharmacological, was evaluated in patients admitted to surgical and internal wards whose risk of venous thrombosis was calculated according to Caprini and Geneva criteria, respectively (Tables 1 and 2).
The primary outcome of the present DUE study included evaluation of the risk of thromboembolic events as well as prophylactic anticoagulation regimens and assessment the compliance of prophylaxis pharmacological and mechanical regimens of patients with these guidelines. The secondary outcome was evaluation of bleeding risk in the patients (Table 3).

Quantitative data were presented as mean and standard deviation (SD), and qualitative data were presented as frequency and percentage. Statistical analysis of the information was performed using PSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation). Student T-test and Chi-Square tests were used to compare quantitative and qualitative data between different groups, and finally, a P value less than 0.05 was considered statistically significant.
Table 3. Risk factors for bleeding.

| Risk factor for bleeding                        | Score |
|------------------------------------------------|-------|
| Moderate Renal failure (30 < GFR < 60)         | 1     |
| Male sex                                       | 1     |
| Age 40-84 years                                | 1.5   |
| Active cancer                                  | 2     |
| Rheumatic disease                              | 2     |
| Central venous catheters                       | 2     |
| Admissions in Intensive Care                   | 2.5   |
| Severe Renal failure (GFR < 30)                | 2.5   |
| Liver insufficiency (INR > 1.5)                | 2.5   |
| Age ≥ 85                                       | 3.5   |
| Thrombocytopenia (<50 × 10^9)                  | 4     |
| Recent (3 months) bleeding                     | 4     |
| Active gastro-intestinal ulcer                 | 4.5   |

Risk category

| Risk category  | Score |
|----------------|-------|
| Low risk       | 0-7   |
| High risk      | >7    |

GFR: glomerular filtration rate, INR: international normalized ratio

Results

A total of 300 patients was included in the study. The mean age of patients was 56.1 ± 19.3 years, with a male majority of 58.3%. Among them, 150 individuals with a mean age of 53 ± 22.2 were admitted in internal wards, and the remaining 150 patients with a mean age of 59.7 ± 18.7 were admitted in surgical wards. Baseline demographic and clinical data of the patients have been summarized in Table 4.

The mean risk of thromboembolic events of patients in internal and surgical wards were 3.3 ± 2 and 11.9 ± 4.6, respectively. Also, the mean calculated bleeding risk in the internal and surgical medicine wards were 3.9 ± 2.6 and 4.1 ± 2.6, respectively (P= 0.95). In this regard, 10.6% of patients in the internal wards and 11.3% in the surgical wards were at high risk of bleeding (Figure1).

Figure 1. The risk of thrombosis and bleeding in the internal and surgical wards.
Among all the patients in both internal and surgical wards, 39 (13%) patients received no prophylactic treatment. While, mechanical prophylaxis methods, including compression stockings and intermittent pneumatic compression devices, were used in 137 (45.6%) patients. Moreover, 248 (82.6%) patients received either of heparin (45.9%) or enoxaparin (36.6%) (Table 4).

Evaluation of the pharmacological and mechanical methods indicated that there was no statistically significant difference in the rate of compliance with the guidelines between the internal and surgical wards (90 (60%) vs. 85 (56.6%); P=0.31).

In the internal wards, the use of the mechanical method was in accordance with Geneva guidelines only in 75 (50%) patients. Mechanical methods were used incorrectly in 12 (8%) patients with no need to receive anticoagulant prophylaxis.

Among the patients in the surgical wards, the mechanical methods administration was based on the Caprini guideline in 99 (66%) patients. While, in 47 (31.3%) patients with a definite indication, the mechanical methods were not used. In opposition, 4 (2.7%) patients with an indication for administration of one prophylactic method, both pharmacological and mechanical methods, were used inappropriately.

There was a significant difference regarding the guideline-based use of mechanical methods between the internal and surgical wards (75 (50%) vs. 99 (66%); P <0.01).

In the internal wards, the administration of pharmacological prophylaxis regimens has consisted with the Geneva guideline in 85 (56.6%). Moreover, 55 patients with no indication for prophylactic anticoagulation received the medicines wrongly. In contrast, 8 cases with a definite indication for prophylactic anticoagulation receive no medication.

Among the patients in the surgical wards, 116 (77.3%) patients received the pharmacological prophylaxis regimens according to the guideline. Among the remaining 34 cases, 30 patients with no indication have prescribed the medicines, and four patients with an indication for one prophylactic method received both of them.

Furthermore, comparing the principles of prophylaxis within the surgical and internal wards showed that the amount of correct administration in drug prophylaxis is significantly higher than the correct administration of mechanical methods in the surgical wards (P=0.02); however, no significant difference was observed in the internal wards (P = 0.10).

Table 4. Demographic and clinical data of patients in the surgical and internal wards

|                          | Surgical ward (mean ± SD) | Internal ward (mean ± SD) | P Value |
|--------------------------|---------------------------|---------------------------|---------|
| Age (year), mean ± SD    | 53±22.2                   | 56.1±19.3                 | 0.91    |
| Risk of thrombosis, mean ± SD | 11.9±4.6             | 3.3±2                     | -       |
| Risk of bleeding, mean ± SD | 4.1±2.6               | 3.9±2.6                   | 0.95    |
| Sex (male), n (%)        | 100 (66.6%)               | 75 (50%)                  | 0.0003  |
| Prophylaxis              |                           |                           |         |
| Mechanical method, n (%) | 103 (68.6%)               | 34 (22.6%)                | 0.0001  |
| Pharmacological          |                           |                           |         |
| • Not prescribed, n (%)  | 30(20%)                   | 19(12.6%)                 |         |
| • Heparin, n (%)         | 66 (44.7%)                | 72 (47.9%)                | 0.23    |
| • Enoxaparin, n (%)      | 53 (35.3%)                | 57 (38%)                  |         |
| Prophylaxis treatment, n (%) | 149 (99.3%)          | 141 (94.1%)               | 0.01    |
Discussion

The present DUE study showed that in spite of the existence of guidelines regarding the administration of pharmacological and non-pharmacological treatment in the prevention and treatment of thromboembolic events, considerable inappropriate administration of heparin/enoxaparin and mechanical prophylaxis for thromboembolic events took place in our hospital.

Previously, some studies have shown that anticoagulation administration is not according to the standard guidelines. Khalili et al., in a cross-sectional prospective study on 400 patients in cardiac care unit, infectious disease, nephrology, and cardiology units demonstrated that 55% of participants have indication to administrate anticoagulants prophylaxis against thromboembolic events. Besides, data analysis showed that the doses of enoxaparin and heparin were inappropriate in 21% and 25% of cases, respectively. Moreover, in 2.8% of individuals, heparin and enoxaparin were ordered inappropriately (12). Furthermore, Pressis et al., conducted a prospective, observational study on a total of 352 patients in South African hospital to evaluate adherence to guidelines for thrombosis prophylaxis events prophylaxis. The appropriate decision to prescribe anticoagulants was made in 72.2% of patients (13). In our study, the administration of pharmacological methods was not based on guidelines in approximately 34% of patients. It is possible that the current discrepancy in the treatment of patients in our study with clinical guidelines and venous thrombosis risk calculation systems and the proposed treatment resulting from physicians’ decisions taking into specific clinical conditions. There were patients who were probably not included in the questionnaires. Also in the study entitled ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) conducted a large-scale study of 68,000 patients in 32 countries. The results of the study indicate that 58.5% of patients were admitted to surgical wards, and only in 39.5% of patients in inpatient wards, effective prevention of venous thrombosis was performed based on clinical guidelines (14). Compared to the results of our study, the prophylactic adaptation rates of patients in both internal medicine and surgery wards were lower than the above study because the adaptation rates in the internal medicine and surgery wards were 60% and 56.6%, respectively.

In another study, Pinjala stated that among patients admitted to surgical and internal wards in India, 16.3% and 19.1% of patients received appropriate prophylactic treatment to prevent venous thrombosis (15). However, the results of our study showed better adherence to clinical guidelines for venous thrombosis prophylaxis compared to the present study. However, in a similar study in France conducted by Bergmann et al., Statistics showed that 53.5% of patients admitted to internal wards and 71.2% of patients admitted to surgical wards underwent a proper venous thrombosis prevention regimen, which was significantly higher than in our study (16).

In another study, Nimeri et al., examined the incidence of venous thrombosis in hospitalized patients over a five-year period, in which the use and adherence of physicians to venous thrombosis risk assessment systems were also evaluated. The results of this study revealed that the rate of following and using the clinical guideline for venous thrombosis prevention was initially less than 80%, which increased to 100% after the launch of the hospital system for assessing the risk of venous thrombosis, which has been associated with a significant reduction in the incidence of venous thrombosis in patients (17). Consequently, considering the results of our study, setting up decision-making systems for venous thrombosis prophylaxis in hospitalized patients is becoming more important.

Similarly, Cardoso et al., examined the incidence of venous thrombosis in patients admitted to the internal and surgical wards, in which the compliance of physicians’ decision to provide venous thrombosis prophylaxis with clinical guidelines was assessed. The results of this study showed that the rate of adherence to the clinical guideline for the prevention of venous thrombosis in 2014 compared to 2010 increased by more than 11% and increased from 63.8% to 75%, which followed the launch of the program. Prevention of patients with venous thrombosis has been done using clinical guidelines (18).

According to the results of the present study, it can be concluded that substantial inappropriate administration of heparin/enoxaparin and mechanical prophylaxis for thromboembolic still occurred in the internal and surgical wards. However, it seems necessary to establish decision-making systems for venous thrombosis prophylaxis in the study center due to non-compliance with VTE standard guidelines in clinical wards.

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References

1. Hull RD, Lip GY, Leung LL. Venous thromboembolism: anticoagulation after initial management. Available from: https://www.uptodate.com/contents/venous-thromboembolism-anticoagulation-after-initial-management. Updated 05, 2020, Accessed 06, 2021.

2. Pai M, Douketis J. Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults. Literature review current through. Available from: https://www.uptodate.com/contents/prevention-of-venous-thromboembolic-disease-in-acute-ill-hospitalized-medical-adults. Updated 07, 2020, Accessed 06, 2021.

3. Pai M, Douketis J. Prevention of venous thromboembolic disease in surgical patients. Available from: https://www.uptodate.com/contents/prevention-of-venous-thromboembolic-disease-in-adult-nonorthopedic-surgical-patients.
4. Geerts WH, Code KJ, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med 1994;331(24):1601-6.
5. Chen Y, Shao J, Zhu W, Jia LS, Chen XS. Identification of risk factors for respiratory complications in upper cervical spinal injured patients with neurological impairment. Acta Orthop Traumatol Turc 2013;47(2):111-7.
6. Francis CW. "Prevention of venous thromboembolism in hospitalized patients with cancer." J Clin Oncol 2009;27(29):4874-80.
7. Deng J, Thomas L, Li H, Vrugtjeskutty E, et al. Overuse of DVT Prophylaxis in Medical Inpatients. Blood 2015;126(23):5563.
8. Minami CA, Yang AD, Je M, et al. Evaluation of an institutional project to improve venous thromboembolism prevention. J Hosp Med 2016;11:829-837.
9. Amin Mansour B, Esraghni N, Abrishamkar S, Torkashvand M, Asnaashari A. Comparing the effect of unfractionated heparin and low molecular weight heparin in preventing of deep vein thrombosis prophylaxis after craniotomy in patients with brain tumor. Journal of Shahrekord University of Medical Sciences 2013;15(3):273-276.
10. Spirk D, Nendaz M, Aujesky D, et al. Predictors of thromboprophylaxis in hospitalised medical patients. Explicit ASsessment of Thromboembolic Risk and Prophylaxis for Medical PATients in SwitzErland (ESTIMATE). Thromb Haemost 2015;113(5):1127-34.
11. Motte S, Samama CM, Guay J, et al. Prevention of postoperative venous thromboembolism. Risk assessment and methods of prophylaxis. Can J Anesth 2006;53:S68-9.
12. Khalili H, Dabih-Khavidaki S, Talasaz A, Najmedin F, Hoseinpoor R. Anticoagulant Utilization Evaluation in a Teaching Hospital: A Prospective Study. J Pharm Pract 2010;23(6):579-584.
13. Du Plessis JA, Van Blydenstein SA, Wong M. Evaluation of the use of low-molecular-weight heparin for venous thromboembolism prophylaxis in medical patients. S Afr Med J 2020;110(3):235-242.
14. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371(9610):387-94.
15. Pinjala R; ENDORSE-India investigators. Venous thromboembolism risk & prophylaxis in the acute hospital care setting (ENDORSE), a multinational cross-sectional study: results from the Indian subset data. Indian J Med Res 2012;136(1):60-7.
16. Bergmann JF, Lloret-Linares C, Rami A, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): results obtained in France. Presse Med 2011;40(12 Pt 1):e528-37.
17. Nimeri AA, Gamaleldin MM, McKenna KI, Turin NP, Mustafa BO. Reduction of venous thromboembolism in surgical patients using a mandatory risk-scoring system: 5-year follow-up of an american college of surgeons national surgical quality improvement program. Clin Appl Thromb Hemost 2017;23(4):392-396.
18. Cardoso LF, Krokoscz DV, de Paiva EF, et al. Results of a venous thromboembolism prophylaxis program for hospitalized patients. Vasc Health Risk Manag 2016;12:491-496.