

ORIGINAL RESEARCH

Evaluation of Association between duration of Hospitalization in-Patient with Deep Venous Thrombosis and the type of Treatment Considering the Effect of Comorbid Diseases

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Abstract: Introduction: Deep vein thrombosis (DVT) is a common disease with serious risks such as pulmonary embolism and there are different anticoagulant therapies for treatment of this condition. In this study, we investigated the association between the duration of hospitalization with different treatment methods and comorbidities. Materials and methods: In this retrospective cross-sectional study, the hospital records of 213 patients with a diagnosis of acute DVT in Shohada-e-Tajrish Hospital in 2019 and 2020 were reviewed. Patients were divided into five main groups and five subgroups based on the type of treatment. Then, the association between the duration of hospitalization and different treatment methods was studied. Results: Treatment with novel oral anticoagulants (NOACs) with an average length of 2.5 days of hospitalization significantly reduces the duration of hospitalization. Combination therapy with low molecular weight heparin (LMWH) and warfarin or LMWH alone, with an average of 8.38 and 8.20 days, is preferable to treatment with unfractionated heparin (UFH) and warfarin, with an average of 9.2 days. Warfarin treatment with an average duration of hospitalization of 8.43 days is in the third place. The use of other methods has increased the duration of hospitalization. History of comorbidities including history of hospitalization, hypertension, smoking, cancer and trauma are the five comorbidities that have the greatest effect on the length of hospitalization of patients, respectively. Conclusion: According to the present study, treatment with NOACs reduces the duration of hospitalization of patients more than the other treatment methods. The second best choice is LMWH injection therapy and continuation with warfarin or starting and continuing treatment with LMWH preferable to injecting treatment with UFH and continuing with warfarin. The type of underlying disease and comorbidities had a significant effect on the duration of hospitalization.

Keywords: Anticoagulants; Deep vein thrombosis; Hospitalization

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1. Introduction

DVT and pulmonary thromboembolism (PTE) are part of the spectrum of venous thromboembolism (VTE), which is the third leading cause of death from cardiovascular disease after myocardial infarction and stroke. (1) Classic clinical signs include edema, limb pain, tenderness, warmth, and erythema of the skin around the site of thrombosis, respectively. Due to the asymptomatic nature of many DVTs that occur in



the hospital, the clinical diagnosis is unreliable. Therefore in addition to clinical scoring systems, ultrasound and D-Dimer measurement can be used. Long-term side effects include recurrent VTE, pulmonary embolism, chronic thromboembolic pulmonary hypertension and post thrombotic syndrome (PTS). (2, 3) Nine studies of hospital records and Asian databases reported VTE rates ranging from 11 to 88 per 10,000 admissions. Population-based estimates for postoperative DVT rates range from 0.15 to 1.35 percent. The elderly are at higher risk of DVT and VTE. (4) Malignancies, pregnancy, OCP or HRT use during menopause, obesity, surgery, trauma, antiphospholipid syndrome, systemic hypertension, COPD, chronic kidney disease, prolonged air travel, blood transfusion, smoking, and air pollution are some of the most common predisposing factors of thrombosis. (5, 6) Due to lifestyle changes and increased immobility, obesity, chronic diseases and cancers will have an increase in incidence in the future. Early diagnosis and treatment of DVT is important and reduces complications such as post-phlebitis syndrome and mortality.

In general, VTE treatment is divided into two categories of primary therapy, including thrombolytic or embolectomy and secondary therapy, including anticoagulants and IVC filter implantation. The basis of VTE treatment is anticoagulants, but the primary method is used for extensive femoral or iliofemoral thrombosis, DVT of the upper extremities or high-risk patients with pulmonary embolism. Anticoagulants are used to prevent and treat DVT, which prevent clots from forming or spreading by blocking the coagulation factors' action. (6) NOACs, including factor Xa inhibitors such as apixaban, edoxaban, and rivaroxaban, and thrombin inhibitors such as dabigatran have been studied in phase three studies in a wide range of thromboembolic disorders (7). The addition NOACs to the pharmacopoeia is one of the most important recent advances in DVT management. Its use has been considered worldwide, although drug selection, recurrence, and chronic therapeutic effects are discussed. Extensive studies are underway to evaluate the effect of NOACs on disease complications such as recurrent thrombosis and post-phlebitis syndrome (PTS) (8, 9). Common anticoagulants such as VKAs, UFH, LMWH have been used for decades but they increase the risk of bleeding. Therefore, NOACs drugs include direct inhibitors of thrombin and direct inhibitors of factor Xa, which have many advantages over conventional drugs, such as rapid impact, low drug and food interactions, no need for routine monitoring such as INR checks, also they have better patient compliance and similar or better efficacy and safety than heparin or VitK antagonists. (10)

In choosing the treatment method of VTE and the type of anticoagulant, factors such as patient's age, risk of bleeding, history of surgery and comorbidities such as cancer, and

kidney failure should be considered. Therefore, the clinical benefits of an anticoagulant should be ideally balanced with the risks associated with treatment (7). DVT treatment algorithms have made great progress in recent years; yet it is necessary to review and compare traditional and new therapies. On the other hand, the economic burden of DVT and PTE on direct medical costs is very high. This is due to the initial hospitalization of patients as well as the readmission of patients (5% -14%), more than half of which occur within 90 days. (11) And due to the existing limitations such as hospital beds and human resources and different therapeutic effects of different methods, choosing the optimal method is important according to the length of hospitalization of patients.

In a 2018 study by Karl E Minges et al., 726,423 patients were admitted from 1999 to 2010 for DVT. In general, the rate of hospitalization in DVT has decreased except in black patients. This decrease has been attributed to changes in treatment protocol and increase in outpatient treatment and faster transfer of hospitalized patients to continue outpatient treatment. (12)

Therefore, in the present study, we decided to examine the patients admitted to Shohada-e-Tajrish Hospital who were hospitalized with this diagnosis during 2019 and 2020 in terms of the length of their hospitalization, and evaluate its association with the type of treatment used and the type of comorbid diseases.

2. Materials and Methods

In this retrospective study, the medical records of 213 patients (122 men, 56.8%) admitted with diagnosis of acute DVT confirmed with Doppler ultrasonography in Shohada-e-Tajrish Hospital in 2019 and 2020 were used to investigate the duration of hospitalization and its association with treatment and the comorbidities of the patients. The study was approved by the ethics committee, and Due to Helsinki convention, name and personal information of the patients will remain confidential with the researchers, all reports will be generalized and nameless.

After receiving the permission of the hospital ethics committee, questionnaires were designed to collect patients' information from their medical records including general information of the patient, history and clinical findings, laboratory and paraclinical findings of the patient, the treatment method used during hospitalization and after discharge, and the presence of comorbidities including ischemic heart disease (IHD), Dyslipidemia (DLP), hypertension (HTN), benign prostatic hyperplasia (BPH), diabetes mellitus (DM), cancer, chronic obstructive pulmonary disease (COPD), cancer, obesity, history of hospitalization, history of surgery, trauma, smoking or oral contraceptives (OCPs) use.

Patients were divided into five main groups and five sub-

groups based on the type of anticoagulant treatment used. The 5 main treatment groups included: NOAC treatment, initiation of injection therapy with UFH and continuation with warfarin, initiation of injection therapy with LMWH and continuation with warfarin, initiation of treatment with UFH and continuation with LMWH and initiation of treatment with UFH and continuation with LMWH. Subgroup groups included: untreated group, mechanical treatment with IVC filter, initiation and continuation of treatment with UFH, continuation of warfarin treatment in patients with relapse who were treated and the use of different anticoagulants (table 1). Mean and standard deviation were used to describe quantitative variables and number and percentage was used for qualitative variables. The Mann-Whitney method was used to evaluate the effect of patients' gender on the length of hospital stay. Data distribution was assessed by X² test. Due to the small number of samples and their abnormal distribution, Kruskal-Wallis test (H test) was used to compare the duration of patients' hospitalization in different treatment groups. Mann-Whitney test (U test) was used to compare two groups of patients with and without comorbidities. To investigate the effect of the type of comorbidities on the duration of hospitalization, Friedman's test was used.

SPSS software version 20 was used for statistical analysis of data. P values of 0.05 or less were considered statistically significant.

3. Results

In this study, 213 patients who were hospitalized with a diagnosis of acute DVT were studied, including 122 (56.8%) males and 91 (43.2%) females, with a mean age of 57.86±19.63.

According to the table 2, 71.8% of patients with DVT presented with typical symptoms of the disease, including swelling, pain and limb erythema, and 28.2% of patients were hospitalized due to other common diseases, and finally the diagnosis of DVT was made. The most common in terms of frequency are loss of consciousness (LOC) with 9%, weakness with 2.8% and shortness of breath with 2.8%, respectively.

Our results showed that gender has no significant effect on length of hospital stay (P value = 0.283). Days of hospital stay in different treatment groups are mentioned in table 3 and the results showed that the treatment method has a significant effect on the length of hospital stay of patients with DVT (P value=0.014) (Diagram 1). Among all of the patients, 101 patients did not have any of the comorbidities considered in the study and 112 had at least one. Mann-Whitney test showed that having comorbidities is significantly associated with the length of hospital stay (P value=0.017). The type of comorbidity has a significant and variable effect on the duration of hospitalization (P value<0.001) (Table 4). In addition, five comorbidities which have the greatest effect on

patients' duration of hospitalization are respectively the history of hospitalization, recent history of surgery, hypertension, smoking and cancer.

4. Discussion

The aim of this study was to evaluate the duration of hospitalization and its relationship with the treatment used and comorbidities in patients admitted with acute DVT diagnosis. From the statistical analysis of the obtained results, it can be concluded that gender has no significant effect on the duration of hospitalization of patients, while the presence of the comorbidities have an effect on the length of hospitalization. Also, the type of treatment affects the duration of the patient's hospitalization, in a way that treatment with NOACs has the shortest duration of hospitalization and in the next ranks are injectable treatment with LMWH or start treatment with LMWH and continue with warfarin, continue warfarin treatment in patients who already have INR impairment and have been treated with warfarin, start treatment with UFH and continue with oral warfarin treatment, installation of IVC filter, using the mix method means starting with UFH, switching to LMWH and continuing with warfarin, UFH treatment alone and start treatment with UFH and continue with LMWH, respectively.

In the study of Y. Hong et al., Which was a systematic review of randomized control trials, 4064 patients were studied. In this study, the effect of anticoagulant therapy on the rate of hospitalization and duration of hospitalization in patients with DVT was investigated. Results of this study depict that, patients treated with LMWH were hospitalized 33% less than UFH and the mean difference in duration of hospitalization between LMWH and UFH was 2.54 days. Also, the duration of hospitalization of patients receiving rivaroxaban was significantly reduced compared to injectable treatments, in a way that this difference was reported 1-5 days for VTE, 3 days for DVT and 1 day for PE. These findings confirm the results of our research. (1)

In an observational study, R. Morillo et al., assessed the hospitalization process and the use of interventional therapies among 26,695 patients with DVT between 2001 and 2014. The average duration of hospitalization decreased from 9.0 days in 2001 to 2005 to 7.6 days in 2010 to 2014, and the rate of LMWH use at the start of DVT treatment decreased from 98% to 90%, while DOACs consumption increased from 0.5% in 2010 to 13.4% in 2014. (13)The findings of this study also show the effect of DOACs on reducing the duration of hospitalization of patients.

In a study by K. E. Minges et al. in 2018, 726,423 patients were admitted from 1999 to 2010 for DVT. In general, the rate of hospitalization in DVT has decreased, except in patients with African origin. This decrease has been attributed to the



change of treatment protocol and the increase of outpatient treatment and faster transfer of hospitalized patients to continue outpatient treatment. (12)

In a 2019 retrospective study by E. R. Pritchard et al., Cancer patients treated with DOACs, LMWH, or Vit K antagonists had an equal risk for major bleeding, with gastrointestinal bleeding being the most common event. The risk of recurrence of VTE in DOACs and LMWH groups was higher compared to previous studies. (14) The difference between the results of this article and our study can be attributed to the focus of this study on cancer patients who may respond differently to anticoagulant therapy.

A 2009 study by N. Isma et al. Examined risk factors and the distribution of VTE. Of the 1140 patients with VTE in 1998-2006, 49% were male and 51% were female. 882 patients had DVT, 330 had PE and 72 had DVT / PE. The most common acquired risk factor for VTE was hormone therapy. Immobility, history of surgery, cancer and family history were also observed in these patients, respectively. (15)

One of the limitations of this study is the retrospective nature of it, so it is not possible to intervene in patients and evaluate changes. Also, oral therapies were not widely used in the years 94 to 95, and therefore the number of samples was not evenly distributed and more accurate comparisons were not possible.

In order to better compare the treatment methods, we propose a prospective study with the aim of examining acute complications such as disease recurrence and bleeding within 90 days after treatment, mortality, post-thrombophlebitis syndrome and the degree of patients' cooperation in taking drugs. Further specific studies are also needed to evaluate the efficacy and safety of anticoagulants, especially NOACs, for the treatment of DVT in specific patient populations, including the elderly, obese, and cancer patients.

5. Conclusion

NOACs, including direct thrombin inhibitors and direct factor Xa inhibitors, have many advantages over older drugs. According to the present study, treatment with these drugs significantly reduces the duration of hospitalization of patients. History of comorbidities including history of hospitalization, hypertension, smoking, cancer and trauma are the five comorbidities that have the greatest effect on the duration of hospitalization of patients, respectively. Because of these comorbidities that cause DVT, it is important to consider prophylactic anticoagulant therapy in high-risk patients.

6. Appendix

6.1. Acknowledgment

None.

6.2. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

6.3. Funding and support

None

6.4. Author's contributions

All the authors had the same contribution.

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Table 1: Frequency distribution of different treatment groups of the study.

	Frequency	Percent	Valid Percent	Cumulative Percent
untreated group	6	2.8	2.8	2.8
NOAC	4	1.9	1.9	4.7
UFH to Warfarin	93	43.7	43.7	48.4
LMWH	24	11.3	11.3	59.6
UFH	4	1.9	1.9	61.5
LMWH to Warfarin	50	23.5	23.5	85.0
IVC Filter	5	2.3	2.3	87.3
different anticoagulants	8	3.8	3.8	91.1
UFH to LMWH	12	5.6	5.6	96.7
Warfarin	7	3.3	3.3	100.0
Total	213	100.0	100.0	

Table 2: The frequency of primary cause of hospitalization of patients with deep vein thrombosis.

	Frequency	Percent	Valid Percent	Cumulative Percent
DVT signs	153	71.8	71.8	78.9
Dyspnea	6	2.8	2.8	81.7
LOC	9	4.2	4.2	92.5
Weakness	6	2.8	2.8	100.0
Total	213	100.0	100.0	

Table 3: The mean of hospital stay (days) in different treatment groups.

Treatment groups	Mean	N	Std. Deviation
Untreated group	19.83	6	30.189
NOAC	2.50	4	1.732
UFH to Warfarin	9.80	93	7.376
LMWH	8.38	24	5.273
UFH	12.50	4	7.853
LMWH to Warfarin	8.20	50	4.267
IVC Filter	9.60	5	6.986
different anticoagulants	10.63	8	6.278
UFH to LMWH	14.08	12	6.445
warfarin	8.43	7	3.645
Total	9.68	213	7.996

Table 4: The effect of different comorbidities on duration of hospitalization.

Comorbidities	Mean Rank
IHD	7.28
BPH	6.62
HTN	8.62
DM	7.42
HLP	7.18
Pregnancy	6.52
Trauma	7.58
Cancer	7.75
Smoking	7.98
Surgery History	8.58
OCP	6.85
Hospitalization history	8.88
Obesity	7.05
COPD	6.68

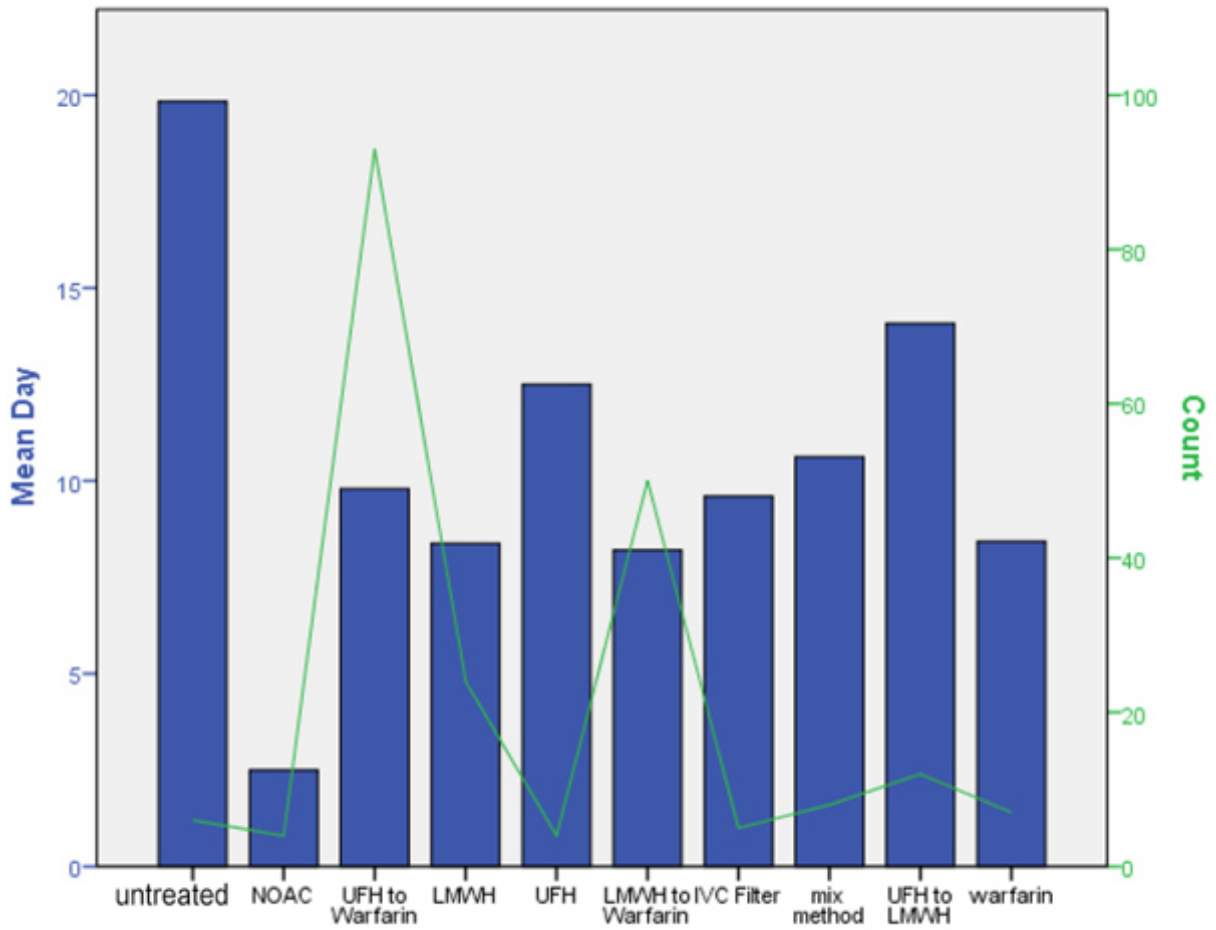


Figure 1: The green bar shows the number of patients in each treatment group and most of the patients underwent treatment with UFH to warfarin. Mean days of hospital stay in each treatment group in showed with blue column and the least was seen in patients treated with NOAC.

