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ORIGINAL RESEARCH ARTICLE

Length of hospital stay in treatment of venous thromboembolism: do outcomes vary according to preference of anticoagulant? A retrospective analysis

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Abstract

Introduction: Regarding the choice of novel or traditional oral anticoagulants for the treatment of different entities of venous thromboembolism (VTE), there is contrasting, little, or no evidence to put forward. We here assess the impact of various anticoagulants in reducing the length of stay (LOS) in patients with acute VTE. Our objectives were: 1) to compare LOS among novel and traditional anticoagulants groups on discharge, and 2) to determine the clinical risk factors responsible for lengthier hospital stay in patients having acute VTE.

Material and methods: We conducted a retrospective data analysis of 161 consecutively admitted patients in the Life line Hospital, Karachi, Pakistan with a recent diagnosis of VTE. Lengths of stay with various anticoagulants on discharge were compared. Bleeding complications and readmission outcomes were compared, along with determination of independent predictors by multivariate analysis for LOS among groups.

Results: Patients discharged on a vitamin K antagonist (warfarin) had significantly longer hospital stays compared to patients on rivaroxaban (7.65 days vs. 5.21 days, p <0.001). Patients discharged exclusively on enoxaparin (hospital stay duration of 3.30 days) or on a combination of enoxaparin and warfarin (hospital stay duration of 4.26 days,) when compared for LOS for rivaroxaban, showed statistical significance (p <0.0001).

Conclusions: Warfarin has significantly longer LOS compared to rivaroxaban. Bleeding outcomes and readmissions compared among anticoagulant discharged groups were found to be statistically insignificant. Novel anticoagulants have an observable impact on the length of hospital stay in patients with acute venous thromboembolism.

Key words: venous thromboembolism, pulmonary embolism, rivaroxaban, enoxaparin, warfarin

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Introduction

Acute venous thromboembolism has long been a grave medical challenge worldwide, and is evidently associated with multiple medical disorders and situations. Deep vein thrombosis (DVT), and pulmonary embolism (PE), either or both, are the typical manifestations of acute venous thromboembolism (VTE), where venous thromboembolism is a frequently encountered ailment, having a yearly incidence of 1 to 2 per 1,000 people [1, 2]. The symptomatology ranges from swelling of an extremity, shortness of breath, to shock or death. Its management depends on the position along with the degree of the VTE, wherein anticoagulation therapy, systemic thrombolysis or thrombolysis via catheterization, and surgical embolectomy, are the most widely used methods. The gold standard in any form of venous thromboembolism is the institution of anticoagulation. The initiation of therapy is with any parenteral agent along with the later introduction of other more novel agents e.g. oral anticoagulants dabigatran, rivaroxaban, or apixaban in a controlled manner under vigilant observation. These agents are far more convenient to use as the need for spanning or tapering has almost been abolished with their introduction to the anticoagulant profile. Although anticoagulants have added positively to the venous thromboembolism armamentarium, there are health and financial challenges. In the USA alone, around 600,000 cases of VTE are admitted yearly and despite appropriate treatment, mortality remains high [3, 4].

Where the early therapy involves parenteral anticoagulation, the goal is to prevent extension and recurrence of any sort of thrombosis [5]. Deep venous thrombosis, although acute, is treated mostly at home rather than in hospital, while pulmonary embolism is an acute medical emergency which is essentially treated in hospital keeping in mind its higher short-term mortality [5]. Conventionally, subcutaneous or intravenous heparin, either low-molecular-weight heparin or unfractionated heparin, is instituted initially combined with a vitamin K antagonist (VKA), often warfarin, given alongside or immediately after the heparin has been initiated [5]. There are many restrictions on the use of VKAs, such as slow-acting warfarin having a narrow therapeutic range and volatile anticoagulation because of various interactions and inconstant metabolism [6]. So, in order to acquire the desired anticoagulation effects, constant monitoring and accurate dose adjustment are mandatory.

As far as the domain of anticoagulants is concerned, there are some more novel and promising agents being offered in the USA, such as dabigatran (a direct thrombin inhibitor), rivaroxaban, edoxaban, and apixaban (factor Xa inhibitors). When compared to the traditional anticoagulants, the newer agents demonstrate swifter inception with few adverse effects and interactions, and a hassle-free follow up investigative routine [6].

As far as management and monitoring in acute venous thromboembolic states such as DVT and PE are concerned, both the EINSTEIN-DVT and EINSTEIN-PE trials have found rivaroxaban to be equally as effective, if not more so, as enoxaparin and warfarin [7–9]. The same EINSTEIN trials, using the inpatient records of admissions retrospectively, revealed a substantially reduced hospital stay in those patients who received anticoagulation through rivaroxaban compared to those who received enoxaparin/VKA [10]. Another Canadian/USA analysis of EINSTEIN-DVT and EINSTEIN-PE patients also established a mean reduction of about 1.6 days in hospital stay for rivaroxaban-treated patients compared to others treated with enoxaparin/VKA [11].

The shorter length of stay, and reduced readmissions, for treatment with rivaroxaban as compared to warfarin and other contemporary agents also has the benefit of being more cost effective. This has been validated by a case-control study over a period of six months [12].

The available data, apart from clinical studies, is scanty to serve the purpose of validating rivaroxaban as a superior anticoagulant. Having seen the evidence of earlier studies from other parts of the world, in an effort to validate the results, we carried out this study aiming to demonstrate the same superiority of rivaroxaban over other anticoagulants in shortening LOS in hospital, improving hassle-free management and monitoring of anticoagulation, as well as reducing the number of readmissions.

Materials and methods

This was a retrospective data analysis of patients consecutively admitted to the Life line Hospital in Karachi, Pakistan with a recent diagnosis of VTE between January and December 2019. All the patients, who had a confirmed diagnosis of VTE, including DVT and PE, were retrieved from hospital records. 161 patients in total having VTE were enrolled for the study duration. Patients aged over 18 years who had a confirmed diagnosis of VTE were included. Patients with evidence of VTE within 24 hours of admission, nosocomial infections, iatrogenic overinfusion, pregnancy, or who had any contraindication to anticoagulation were excluded. Patients with a high risk of PE as evidenced by surgical embolectomy or catheter-delivered systemic thrombolytic or thrombolytic agents were also excluded from the study.

Deep vein thrombosis

The criteria from the American College of Radiology were applied in order to confirm the diagnosis through sonology in accordance with the criteria entailing venous non-compressibility of the involved vein with thrombus echogenicity from within the venous lumen, venous distension of vein, complete Doppler or spectral signal loss from within venous lumen, absent flow phaticity, and muted Valsalva or augmentation response [13].

Pulmonary embolism

Patients suspected for pulmonary embolism were stratified by using a modified Wells Score [14]: >4 for a likely diagnosis, <4 for unlikely, along with D dimer level. Patients with a modified Wells Score >4 were further confirmed objectively via a computerized tomography pulmonary angiogram (CTPA). Pulmonary embolism was confirmed by the following criteria [15, 16] on CTPA:

- A large filling defect due to arterial occlusion and enlarged size with respect to adjacent vessels;
- A 'polo mint' sign (a partial filling defect enclosed by contrast material) evidenced on images attained vertical to the long axis of a vessel and a 'railway track' sign (demonstrated on vertical images of the vessel);
- Acute angles formed with the arterial wall due to a peripheral intraluminal filling defect.

Primary and secondary outcomes

The primary outcome of our study was length of stay in hospital. Bleeding complications, either during index admission or on subsequent readmission, were considered as the secondary outcome.

Bleeding complications

Bleeding complications were defined and classified in accordance with a previously published study [17] where patients had central nervous system bleed, a fall of hemoglobin level to >2 g/dL, and the prerequisite transfusion of two or more packed cell units. Patients who did not meet the major bleeding criteria were labeled as having minor bleeding complications.

Statistical analysis

Demographic features and clinical physiognomies of the patients on different anticoagulants were shown with their frequency, means ±standard deviation or median (inter-quartile range). For comparison among the groups, one-way analysis of variance (ANOVA), Kruskal-Wallis test and exact Pearson's Chi-square test were applied as required. Statistical association between anticoagulants and length of stay in hospital among the patients having VTE were determined by Kruskal-Wallis test. For multiple comparison of length of hospital stay within four types of anticoagulant discharge medication in patients having VTE, Bonferroni's adjustment was applied. A Wilcoxon test was used for variables (categorical) having two categories. For multiple categories of categorical variables among groups, we used a Kruskal-Wallis test.

Results

In our study, multiple demographic and clinical risk factors were taken into account and statistically analyzed for prolonged hospital stay or outcome with treatment of VTE with various anticoagulation agents.

Demographic parameters

Among demographic profiles, the mean ages of patients on rivaroxaban, on warfarin, on both enoxaparin and warfarin, and on enoxaparin alone, were 60.02 ±10.4, 55.50 ±14.68, 59.69 ±11.54, and 56.37 ±13.46 years respectively. Of the 161 patients, there were 71 (44.09%) males and 90 (55.90%) females in all groups. Gender distribution and ages among various groups are set out in Table I.

Clinical risk factors

Nearly half of the patients, 69/161 (42.8%), were discharged on warfarin, where patients with DVT and DM were in the majority. 49/161 (30.43%) patients were discharged on rivaroxaban as an anticoagulant, where the majority of patients had DVT, DM and malignancies. 30 patients (18.6%) were discharged on combined enoxaparin and warfarin, with the majority having DM and DVT. Various clinical risk factors such as gender, age, hyperthrombophilic state, malignancies, hormones, immobilization, chronic liver disease (CLD), congestive cardiac failure (CCF), acute coronary syndrome (ACS), chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), deep vein thrombosis (DVT), and PE alone were compared among all four groups of anticoagulation discharge with reference to the length of hospital stay, as shown in Table I. Hyperthrombophilic state (p <0.001), deep vein thrombosis (p <0.012), COPD (p <0.001), and CKD (p <0.028) were found to be statistically significant for prolonging the length of stay in hospital among the groups discharged on anticoagulants, as shown in Table I.

Discharged anticoagulants and length of hospital stay

A significant overall statistical association (p <0.001) was found between duration of stay in hospital and various anticoagulants on discharge such as rivaroxaban, warfarin sodium, enoxaparin with warfarin, and enoxaparin alone. Patients who were discharged on anticoagulation with warfarin had significantly longer LOS compared to those sent home on rivaroxaban (7.65 vs. 5.21 days, p <0.001; Table II). Patients who were discharged exclusively on enoxaparin (3.30 days), or enoxaparin and warfarin (4.26 days), when compared for length of stay with rivaroxaban, also showed statistical significance (p <0.0001).

Outcome measures

Bleeding complications

Bleeding complications were assessed and compared as an outcome through univariate analysis among the discharged anticoagulant patients. Major bleeding complications appeared in five (10.9%) patients on rivaroxaban, seven (10.1%) with warfarin, two (6.7%) on enoxaparin plus warfarin therapy, and in 0 (0%) enoxaparin-taking patients. Mild

Table I. Length of Stay among patients discharged on various anticoagulants (clinical risk factors)

Groups	Warfarin (69)		Enoxaparin and warfarin (30)		Rivaroxaban (46)		Enoxaparin (16)		*P*-value
Age (years)	55.50 ±14.68		59.69 ±11.54		60.02 ±10.49		56.37 ±13.46		
Male	27	23	50.0%	39.1%	13	43.3%	8	50.0%	0.665
Hormones	1	1	2.2%	1.4%	3	10.0%	1	6.2%	0.181
Immobilization	3	5	10.9%	4.3%	6	20.0%	2	12.5%	0.113
Hyper thrombophilia	4	6	13.0%	5.8%	9	30.0%	11	68.8%	<0.001
Malignancy	8	10	21.7%	11.6%	9	30.0%	4	25.0%	0.148
Surgery	5	3	6.5%	7.2%	2	6.7%	2	12.5%	0.878
Post traumatic	1	4	8.7%	1.4%	1	3.3%	2	12.5%	0.154
Surgery	5	3	6.5%	7.2%	2	6.7%	2	12.5%	0.878
Congestive heart failure	4	3	6.5%	5.8%	6	20.0%	1	6.2%	0.114
Diabetes mellitus	22	18	39.1%	31.9%	15	50.0%	8	50.0%	0.284
Chronic kidney disease	7	6	13.0%	10.1%	10	33.3%	2	12.5%	0.028
Chronic obstructive pulmonary disease	4	3	6.5%	5.8%	1	3.3%	7	43.8%	<0.001
Chronic liver disease	1	2	4.3%	1.4%	1	3.3%	1	6.2%	0.707
Pulmonary embolism alone	1	2	4.3%	1.4%	2	6.7%	2	12.5%	0.227
Deep vein thrombosis	64	44	95.7%	92.8%	30	100.0%	12	75.0%	0.012
Unknown	31	20	43.5%	44.9%	13	43.3%	4	25.0%	0.533

Table II. Correlation of outcomes with various anticoagulants on discharge

Groups	Warfarin sodium		Warfarin with enoxaparin		Rivaroxaban		Enoxaparin alone		*P*-value
Length of Stay (days)	7.65 ±1.29		4.26 ±1.01		5.21 ±1.20		3.30 ±1.40		<0.001
Median (inter-quartile range)	7.73 (1.55)		4.35 (1.74)		5.55 (1.98)		3.79 (2.55)		
Readmission	3	4.3%	2	6.7%	3	6.5%	1	6.2%	0.949
Bleeding manifestations									0.802
Major	7	10.1%	2	6.7%	5	10.9%	0	0.0%	
Mild	3	4.3%	1	3.3%	2	4.3%	0	0.0%	
None	59	85.5%	27	90.0%	39	84.8%	16	100.0%	

bleeding was observed in two (4.3%) rivaroxaban patients, three (4.3%) on warfarin, one (3.3%) on enoxaparin plus warfarin, and in none of the enoxaparin-taking patients. Bleeding outcome when compared among anticoagulant discharged groups was found to be statistically insignificant (p <0.802) (see Table II).

Readmissions

Readmissions, as another outcome parameter among these groups, were observed to be three (6.5%) on rivaroxaban, three (4.3%) on warfarin, two (6.7%) on enoxaparin plus warfarin, and one (6.2%) on enoxaparin. When compared, it was statistically insignificant, with a p value of 0.949 (see Table II).

Duration of hospital stay (independent predictors)

Various independent predictors such as age, gender, and conditions such as COPD, CCF, and CKD were assessed by multivariate analysis for Length of Stay among groups of patients discharged on various anticoagulants. Anticoagulants like enoxaparin, enoxaparin + warfarin, and warfarin alone with reference to rivaroxaban were also assessed as independent predictors for Length of Stay among groups of patients. Among all independent predictors for Length of Stay, only the discharged anticoagulants enoxaparin, enoxaparin + warfarin, and warfarin were found to be significant (p <0.001, <0.03 and <0.001) (see Table III).

Table III. Independent predictors of longer hospital stay among patients with different anticoagulants

Predictors	Estimate of regression	Standard error of regression	t	*P*-value	95% confidence interval for B	
					Lower bound	Upper bound
Demography						
Age	–0.00064	0.008	–0.082	0.934	–0.016	0.015
Gender	–0.013	0.202	–0.064	0.949	–0.413	0.387
Anticoagulants						
Warfarin	2.358	0.243	9.723	<0.001	1.879	2.838
Enoxaparin and warfarin	–0.913	0.306	–2.983	0.003	–1.518	–0.308
Enoxaparin	–1.809	0.419	–4.312	<0.001	–2.638	0.980
Clinical risk factors						
Chronic kidney disease	–0.399	0.292	–1.367	0.174	–0.975	0.178
Chronic obstructive pulmonary airway disease	–0.175	0.391	–0.447	0.656	–0.948	0.598
Congestive cardiac failure	–0.221	0.357	–0.619	0.537	–0.927	0.485
Causes of VTE						
Hyper-thrombophilia	0.054	0.305	0.177	0.860	–0.549	0.657
Hormonal	0.180	0.547	0.330	0.742	–0.900	1.261
Malignancy	–0.452	0.261	–1.732	0.085	–0.967	0.064
Immobilization	0.482	0.342	1.411	0.160	–0.193	1.158
Surgery	–0.544	0.392	–1.388	0.167	–1.319	0.231

Discussion

Our study compared the effect of various anticoagulation drugs on patients with VTE. The duration of hospital stay, bleeding, and readmissions were assessed as outcome parameters. Age and gender distribution were compared among anticoagulation groups (warfarin, rivaroxaban, warfarin and enoxaparin, and enoxaparin alone) and found to be statistically insignificant. However, an earlier study [17] has shown age to be statistically significant among anticoagulation groups. The majority of patients in our study were on warfarin, followed by rivaroxaban, enoxaparin + warfarin, and enoxaparin alone, and this is in accordance with an earlier study [17]. Warfarin is the most cost-effective drug among all groups, which explains its being the most used anticoagulant group. Among various clinical risk factors such as thrombophilia, CCF, COPD, and CKD, only hyper-thrombophilic state, deep vein thrombosis, COPD and CKD were statistically significant for prolonging the length of stay in hospital among the discharged groups of anticoagulants.

Ruggles et al. [18] have shown heart failure, CKD and coronary artery disease to be significant clinical risk factors for prolonging hospital stay among patients with thromboembolism on various anticoagulants. A previous similar study [17] has also shown CKD, malignancy and hypercoagulable state as significant risk factors prolonging hospitalization in patients with thromboembolism on anticoagulants. An earlier study [18] among intensive care unit (ICU) patients on anticoagulants had shown length of stay for warfarin to be 3.0 days [95% confidence interval (CI) 1.9–3.9; p <0.001] more than for patients on dabigatran, and 2.4 days longer (95% CI 0.9–3.7; p =0.003) than for patients on rivaroxaban. However, that study showed no difference in hospital stay between rivaroxaban and dabigatran, although it differed from the current study as they also compared novel anticoagulants like dabigatran and rivaroxaban.

Saint et al. [19] compared duration of hospital stay among patients managed through novel oral anticoagulants (rivaroxaban) with warfarin and warfarin plus a parenteral agent for venous thromboembolism. They found a shorter duration of hospital stay (2.63 vs. 5.33 days; p <0.05) for rivaroxaban. Our current study showed slightly more major bleeding in patients discharged on warfarin, although overall comparison of bleeding among various groups of anticoagulants showed no significant difference. When bleeding as an outcome parameter for length of hospital stay was compared among groups, length of stay was shortest with

rivaroxaban. Ruggles et al. [18] also assessed length of stay among patients having bleeding due to various anticoagulant groups, and showed shortest length of stay with dabigatran and rivaroxaban as compared to warfarin. An earlier study [17] reported similar results to our study. Readmission as an outcome parameter in our study did not differ among various groups of anticoagulants, which is similar to the earlier study [17]. Readmission in our study was lower than that reported in the EINSTEIN trial [7]. Rivaroxaban, warfarin, enoxaparin plus warfarin, and enoxaparin alone were found to be significant independent predictors of length of stay in our study. The earlier study found similar results [17].

Conclusions

In our study, various demographic features and clinical characteristics of patients with VTE have been analyzed for consecutive durations of hospital stay, while comparing the impact to the array of contemporary versus novel anticoagulant drugs.

It is noteworthy that patients who were discharged on anticoagulation with warfarin had significantly longer LOS compared to those sent home on rivaroxaban (p <0.001). Bleeding outcome and readmissions when compared among anticoagulant discharged groups were found to be statistically insignificant: p <0.802, and p <0.949 respectively. Among all independent predictors of length of stay, only discharged anticoagulants enoxaparin, enoxaparin +warfarin, and warfarin, were found to be significant (p <0.001, p <0.03 and p <0.001, respectively).

Therefore, our study concludes that the preference of novel anticoagulants has an observable impact on the length of hospital stay in patients with acute venous thromboembolism.

Authors' contributions

IHN and AT: design of study; SNZR: statistical analysis; MR, RZG and SKF: manuscript writing, data collection; AT: final approval

Conflicts of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

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