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Effects of Rivaroxaban on Coagulation Assays in Patients with Small Pulmonary Embolism and Deep Vein Thrombosis in Relation to Body Mass Index

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ABSTRACT

Introduction: Rivaroxaban is a new anticoagulant medication for pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). There are limited data on the effect of body mass index (BMI) on the pharmacokinetics of rivaroxaban. This study aimed to assess the effect of rivaroxaban on coagulation assays in relation to BMI in PTE and DVT patients.

Materials and Methods: the present cohort studywas conducted on patients with DVT and PTE who were planned to receive rivaroxaban (15 mg bid). Demographic characteristics, as well as anthropometric measurements, were recorded before the rivaroxaban administration. Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were measured before and after 4-6 days of treatment with rivaroxaban. The data were analyzed using paired t-test and analysis of covariance in SPSS software, version 20 (IBM Inc., Chicago, Il, USA)

Results: This study was carried out on 100 subjects (i.e., 45 males and 55 females) with the mean age of 38.8±1.7 years. The majority of the subjects (68%) had normal creatinine clearance. The results of the research revealed a significant increase in PT, PT, and INR after the administration of rivaroxaban in both normal-weight and obese subjects (P<0.001 each). Additionally, it was found that the coagulation assays were increased significantly in all age (i.e., <40 and >40 years), gender, and creatinine clearance (i.e., normal and abnormal) groups (P<0.001 each). Furthermore, the final PTT was found to be related to age (P=0.011), while final PT was associated with BMI (P=0.035) and baseline PT (P=0.030).

Conclusion: The findings of this study indicated a significant increase in coagulation assays in both normal weight and obese subjects; however, the final PT increment was reduced by BMI.

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Introduction

Pulmonary thromboembolism (PTE) and deep vein thrombosis are the two common types of venous thromboembolism [1]. The estimated annual incidence of venous thromboembolism in Europe ranges from 104 to 183 per 100,000 individuals [1]; however, this value is higher in African-Americans and lower among Asians. Regarding PTE, the annual incidence rate in the world and Europe

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were estimated at 60-70 and 50-100 per 100,000 people, respectively [2]. However, owing to the fact that many cases of PTE and deep vein thrombosis are asymptomatic, they may not be diagnosed. Accordingly, this figure seems to be lower than the exact incidence of PTE, compared to the reported annual incidence rate of deep vein thrombosis (1-2 per 1,000) [3].

The standard treatment for both conditions is the administration of oral anticoagulants [4, 5]. A new group of anticoagulants are the Non-Vitamin K antagonist oral anticoagulants (NOACs), including rivaroxaban and dabigatran [6]. The NOACs are administered for stroke prevention, acute myocardial syndrome, prophylaxis, both valvular and non-valvular atrial fibrillation, and treatment of PTE or deep vein thrombosis [7]. Rivaroxaban is a 436-g/mol molecule which binds to albumin and acts as a selective inhibitor for the free factor Xa, which is a common member of the internal and external coagulation pathways and has an important role in clot formation [8].

Rivaroxaban is believed to be a fast-acting anticoagulant with a half-life range of 9-13 h [8]. Rivaroxaban is mostly metabolized by the kidney (70%), through cytochrome P450 (CYP450) and CYP2JP, and liver (30%) [9]. Rivaroxaban reaches its therapeutic serum level within 2-4 h after oral administration [10]. Rivaroxaban requires neither dose adjustment based on age and gender nor routine monitoring [8]. Furthermore, there are no reported drug interactions and dietary restrictions for the administration of rivaroxaban [8]. Increased prothrombin time (PT) indicates high plasma concentrations of rivaroxaban; however, PT is not assessed in all cases of rivaroxaban administration [11]. Nevertheless, there is no consensus on the effect of rivaroxaban on PT, partial thromboplastin time (PTT), and international normalized ratio (INR) [12, 13].

Body mass index (BMI) is a measure of weight adjusted for height and is widely used for the adjustment of medication dose [14]. Few studies have been conducted to assess the effect of BMI on coagulation tests in cases on rivaroxaban administration [15-18]. Given the fatal consequences of increased hemorrhage resulting in overtreatment with anticoagulants, the present study was conducted to assess the effect of rivaroxaban on coagulation assays in patients with PTE and DVT in relation to BMI.

Materials and methods

This quasi-experimental study was conducted on ambulatory and admitted patients with the diagnosis of small PTE and DVT referring to Edalatian Emergency Department of the Imam Reza Hospital, Imam Reza Hospital Cardiology Clinic and clinics of Islamic Azad University, Mashhad branch, Mashhad, Iran. The patients were under the administration of rivaroxaban at the time of the study. The research protocol was approved by the Ethical Committee of the Islamic Azad University (IR.IAU.REC.1397.079).

The inclusion criteria entailed: 1) age range of < 8 years old, 2) small PTE and DVT diagnosis by a cardiologist, 3) treatment with rivaroxaban, and 4) BMI of >18.5 kg/m^2. On the other hand, the exclusion criteria included: 1) treatment with other anticoagulant agents (e.g., heparin, enoxaparin, and warfarin) during or in the past 5 days before administration, 2) creatinine clearance level of < 30 ml/min, 3) infliction with hepatic or lymph proliferative diseases, 4) pregnancy or lactation, 5) use of contraceptive medications, and 6) malignancies.

The sample size could not be calculated because of insufficient data on the effect of BMI on coagulation assays in response to rivaroxaban. Accordingly, the study was performed on 100 subjects (i.e., 50 normal weight and 50 overweight/obese subjects) using convenience sampling technique. The eligible subjects were informed about the study and those who were willing to participate were asked to sign a written informed consent prior to participation.

Demographic information and medication history of the subjects were collected from their medical records. The weight and height of the subjects were measured; thereafter, BMI was calculated by dividing weight (kg) by the square of height (m^2). Based on the World Health Organization BMI classification, the subjects with the BMI of 18.5-24.9 and > 25 kg/m^2 were grouped into normal weight and overweight/obese, respectively [18]. In addition, creatinine clearance was calculated for each subject based on the latest laboratory results. All subjects underwent coagulation assays, including PT, PTT, and INR, at baseline (i.e., prior to rivaroxaban administration). Rivaroxaban was administered orally at a dose of 15 mg bid. Coagulation assays were repeated 4-6 h after the initiation of the therapeutic procedure.

Statistical analysis

The data were analyzed in SPSS software, version 20 (IBM Inc., Chicago, Il, USA). The normality of the continuous variables was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. The student paired t-test was used for the comparison of variables between BMI groups. The effect of study parameters on final PT and PTT was assessed using the analysis of covariance (ANCOVA). A p-value of less than 0.05 was considered statistically significant.

Results

The current study was carried out on 100 subjects (i.e., 45 males and 55 females) with the mean age of 38.8±1.7 years. Table 1 presents the baseline characteristics of the study subjects. Based on the results, the majority of the subjects (68%) had normal creatinine clearance. Table 2 shows the changes in coagulation assays after the administration of rivaroxaban. The results of the study were indicative of a significant increase in coagulation assays after the administration of rivaroxaban ($P<0.001$). Comparison of coagulation assays based on the participants' age, gender, creatinine clearance, and BMI are demonstrated in tables 3 and 4. There was a significant increase in all three assays in terms of different BMI and age groups as well as different genders and Creatinine clearance categories ($p<0.01$). (Tables 3 and 4). The effect of study parameters on final PT and PTT are illustrated in Table 5. The ANCOVA analysis revealed that final PT was associated with BMI and baseline PT ($P=0.035$ and $P=0.030$, respectively), while final PTT was found to be related to age ($P=0.011$).

Discussion

As the findings of this study demonstrated, rivaroxaban treatment significantly increased PT, PTT, and INR by 1.75, 1.15, and 2.89 times, respectively, during the first 4-6 h of administration, compared to the baseline As the findings of this study demonstrated, rivaroxaban treatment significantly increased PT, PTT, and INR by 1.75, 1.15, and 2.89 times, respectively, during the first 4-6 h of administration, compared to the baseline values. This finding was in line with the results of a previous study conducted on 80 patients who underwent hip or knee replacement surgery, reporting

Table 1. Baseline characteristics of study subjects

Variable	Mean ± SD
Age (year)	38.8 ± 1.7
Height (cm)	163.3 ± 3.8
Weight (kg)	67.6 ± 3.4
BMI (kg/m2)	25.2 ± 2.1
Creatinine clearance ml/min	83.60 ± 23.45

SD= Standard Deviation, cm= centimeter, kg= kilogram, ml=milliliter, min=minute

Table 2. Changes in coagulation assays in response to rivaroxaban administration

Variable	Baseline Mean ± SD	After 4-6 hours Mean ± SD	Paired t-test	p-value
PT (seconds)	12.71±0.46	22.30±4.07	24.00	<0.001**
PTT (seconds)	32.59±0.49	37.67±2.80	17.96	<0.001**
INR	1.00±0.00	2.89±0.74	25.54	<0.001**

PT= Prothrombin Time, PTT= Partial Thromboplastin time, INR= International Normalization Ratio, SD= Standard Deviation
Paired t-test was used for the comparisons.
** Significant at α=0.01

Table 3. Comparison of coagulation assays between BMI and age groups

Variable		BMI category				Age category			
		Normal	p-value	Overweigh t/obese	p-value	<40 years	p	>40 years	p-value
PT (seconds)	Before	12.68±0.47	<0.001**	12.74±0.44	<0.001**	12.69±0.46	<0.001**	12.73±0.45	<0.001**
	After	23.18±4.30		21.42±3.67		21.73±4.09		23.12±3.95	
PTT (seconds)	Before	32.62±0.49	<0.001**	32.56±0.50	<0.001**	32.53±0.50	<0.001**	32.68±0.47	<0.001**
	After	37.98±3.05		37.36±2.51		37.10±2.56		38.49±2.96	
INR	Before	1.00±0.00	<0.001**	1.00±0.00	<0.001**	1.00±0.00	<0.001**	1.00±0.00	<0.001**
	After	3.08±0.74		2.70±0.69		2.81±0.76		3.01±0.71	

PT= Prothrombin Time, PTT= Partial Thromboplastin time, INR= International Normalization Ratio, SD= Standard Deviation
Paired t-test was used for the comparisons.
** Significant at α=0.01

Table 4. Comparison of coagulation assays between gender and creatinine clearance groups

		Gender				Creatinine clearance			
		Male	p-value	Female	p-value	Normal	p-value	Abnormal	p-value
PT (seconds)	Before	12.80±0.40	<0.001**	12.64±0.49	<0.001**	12.66±0.48	<0.001**	12.81±0.40	<0.001**
	After	23.13±4.02		21.62±4.02		22.66±3.93		21.53±4.32	
PTT (seconds)	Before	32.33±0.48	<0.001**	32.80±0.40	<0.001**	32.71±0.46	<0.001**	32.34±0.48	<0.001**
	After	38.13±3.04		37.29±2.55		37.72±2.63		37.56±3.17	
INR	Before	1.00±0.00	<0.001**	1.00±0.00	<0.001**	1.00±0.00	<0.001**	1.00±0.00	<0.001**
	After	2.99±0.78		2.81±0.70		3.00±0.67		2.66±0.83	

PT= Prothrombin Time, PTT= Partial Thromboplastin time, INR= International Normalization Ratio, SD= Standard Deviation
Paired t-test was used for the comparisons.
** Significant at α=0.01

Table 5. Effect of study parameters on final PT and PTT

Variable	Final PT		Final PTT	
	F	p-value	F	p-value
Age	2.004	0.160	6.718	0.011*
Gender	3.625	0.160	3.204	0.77
BMI	4.553	0.035*	1.766	0.187
Creatinine clearance	1.065	0.305	0.487	0.487
PT before	4.844	0.030*	-	-
PTT before	-	-	0.807	0.371

PT= Prothrombin Time, PTT= Partial Thromboplastin time
Degree of freedom was 1 for all variables.
The analysis of covariance (ANCOVA) was used for the analysis.
** Significant at α=0.05

A two-fold increase in PT and PTT after the administration of rivaroxaban [21].

Furthermore, the currents study revealed a statistically significant difference between the coagulation assays measured before and after rivaroxaban administration in the categories of age, BMI, gender, and creatinine clearance. This result is indicative of the similar effects of these factors on coagulation assays. This finding was consistent with the results of previous studies, which suggested no requirement for dose adjustment in relation to body weight or BMI and age after the administration of rivaroxaban in different patient populations [20-26]. Additionally, it was stated that in obese patients, who lost weight through bariatric surgery, rivaroxaban administration did not show a significant change in INR, compared to phenprocoumon [26].

Moreover, it was also suggested that despite the creatinine clearance reduction in the elderly, the age does not significantly affect the pharmacokinetics of rivaroxaban [23]. In contrast to the findings of the current study, in another

research performed on 14,264 patients with atrial fibrillation, the risk of stroke was compared between patients administered rivaroxaban and warfarin [25]. In this regard, the study reported that despite the similarity of the overall risk of major bleeding, the risk of major bleeding induced by rivaroxaban was related to age and gender [27].

This discrepancy can be attributed to the differences of sample size, study design, and outcome measures. Contrary to the findings of this research, in a previous study, creatinine clearance was found to be the sole predictor of rivaroxaban exposure [27]. In addition, it was stated that nearly one-third of rivaroxaban excreted is eliminated as unchanged into the urine, and this elimination pattern is unique, compared to other direct oral anticoagulants [28]. Therefore, the elimination of rivaroxaban is mainly related to the kidney function [29]. This spotted inconsistency can be related to the inclusion of subjects with higher glomerular filtration rate (GFR) and smaller sample size in our study.

The findings of this study indicated that age was the only predictor of PTT after rivaroxaban administration. As mentioned before, creatinine clearance decreases with age; therefore, it can be hypothesized that the metabolism and elimination of rivaroxaban could be influenced by aging [23, 30, 31]. Moreover, the findings of the current study revealed a statistically significant increase in PTT after the administration of rivaroxaban in both age groups. However, the difference in PTT variations in young and older age groups was not of clinical significance.

Furthermore, the findings of the current study indicated that BMI and baseline PT were associated with the final PT. Although PT increased in both normal weight and overweight subjects, the rate of increase was less in the overweight/obese subjects. This finding revealed that although rivaroxaban is effective in both normal weight and overweight/obese groups, the effects of the medication might be ameliorated in overweight subjects.

It was previously shown that the renal activity increases in obese subjects [28]; therefore, it is hypothesized that creatinine clearance might also elevate with increased body weight, and that the metabolism and elimination of rivaroxaban might increase in obese subjects, which in turn reduces the effects of this medication. It is recommended that other researchers conduct further studies to assess the underlying mechanism of variation in the pharmacokinetics of rivaroxaban in response to weight gain and assess the significance of this effect on the desired effects of rivaroxaban.

Research Limitations

One of the limitations of this study was the small sample size, which could not be determined based on the scarcity of previous studies. It is suggested that further researchers conduct larger studies in order to assess the effect of BMI and creatinine clearance on the metabolism of rivaroxaban more effectively. In addition, further researchers are recommended to carry out other studies on subjects with various renal function so as to assess the necessity of drug dose adjustment in patients with low GFR.

Conclusion

The findings of this study indicated that rivaroxaban can be effective in patients with normal and reduced renal function, as well as normal and overweight/obese subjects, in both genders. Although some differences were found between groups, they were not of clinical significance in most indices, except for BMI in relation

to variation in PT. In addition, this study highlighted the possible effect of obesity on the metabolism of rivaroxaban, which requires further investigation.

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Conflicts of interest

None.

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