Original Research Article

Prevalence of Heavy Menstrual Bleeding in Women Taking Rivaroxaban

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Abstract

Background: Bleeding is a common side effect during anticoagulant therapy. Rivaroxaban, a new anticoagulant, presents concerns regarding its association with heavy menstrual bleeding. *Objectives:* Our aim is to measure the prevalence of heavy menstrual bleeding in women taking rivaroxaban. We aim to measure the median Pictorial Blood Assessment Chart (PBAC) score, and its association with iron deficiency anemia (IDA), passage of clots, and age, respectively. *Methods:* This was a prospective, non- interventional study set in a thrombosis clinic. There were 49 patients enrolled. The study consisted of two parts: a retrospective part regarding collection of menstrual history data before starting rivaroxaban; and a prospective part using validate Arabic PBAC for the next three menstrual cycles. Main outcome measures: Prevalence of heavy menstrual bleeding among women taking rivaroxaban. *Results:* The median PBAC score for women taking rivaroxaban for an average of 3 months was 211, IQR (42.5, 375.9) The prevalence of heavy menstrual bleeding in women taking rivaroxaban was 22%. There is a weak correlation between IDA and age, and IDA and average PBAC score. *Conclusion:* Rivaroxaban may cause heavy menstrual bleeding, but it does not lead to prolongation of menstruation. A detailed menstrual history should be taken before considering rivaroxaban for women in reproductive age.
Keywords: Heavy menstrual bleeding, rivaroxaban, anticoagulation, deep vein thrombosis, pulmonary embolism.

BACKGROUND

Venous thromboembolism (VTE) is a common disease, and deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two most common forms of VTE. It affects 1-10 per 10,000 women of reproductive age [1, 2]. Anticoagulation is the main stay of treatment, and prolonged treatment is required for at least 3 months [3]. Bleeding is a major concern for anticoagulants. The use of direct oral anticoagulants (DOACs) is increasing for the treatment of VTE and non-valvular atrial fibrillation. Rivaroxaban showed comparable safety and efficacy to vitamin K antagonists (VKA) on EINSTEIN-DVT and PE studies [4, 5]. Female gender has been associated with a higher risk of major and clinically relevant non-major bleeding when prescribed anticoagulants, including DOACs [6]. A type of non-major bleeding is heavy menstrual bleeding (HMB), affecting 10–30% of women during some point of their child-bearing years in the absence of anticoagulation therapy [7, 8]. The use of rivaroxaban was associated with prolongation of menstrual bleeding, and an increased need for medical or surgical intervention. In addition, one study [9] suggested that its use required adaptation of anticoagulant treatment due to abnormal uterine bleeding (AUB), as compared to VKAs. In another study, 20% of 128 patients using rivaroxaban reported heavy menstrual bleeding [10], and another study found that 25% of women on rivaroxaban complained of heavy menstrual bleeding [11].

The Pictorial Blood Assessment Chart (PBAC) was initially designed to quantify menstrual blood loss. A score of 100 or more, used to diagnose menorrhagia, found sensitivity and specificity of more than 80% of

those evaluated [12]. In Saudi Arabia, there is no specific data regarding the effect of rivaroxaban on menstrual bleeding.

OBJECTIVES
Primary Objectives
To evaluate the prevalence of heavy menstrual bleeding among women using rivaroxaban.

Secondary Objectives
To evaluate the:
Median score of PBAC on women taking rivaroxaban.
Median duration of menstruation, percentage of clots, iron deficiency anemia (IDA), and intermenstrual and post-coital bleeding before and after anticoagulation.
Correlation between PBAC score and age, IDA.

Design: Observational prospective study

Setting: Thrombosis clinic

MATERIAL AND METHODS
After obtaining scientific and ethical approval from office of research affairs we started our study. First, we followed the guidelines of Tsang [13] in developing, translating, and validating the PBAC to the Arabic language. Then, we tested our proposed Arabic PBAC on 25 women not undergoing anticoagulant therapy.

After that we started the study by screening 57 patients over a period from January until October 2018; 49 patients met the inclusion criteria.

Inclusion criteria
We included Saudi women aged from 14 to 55 years who were not menopausal, and who had been administered rivaroxaban for the last one month for deep vein thrombosis (DVT), pulmonary embolism (PE), or atrial fibrillation.

Exclusion Criteria
We excluded women who had undergone hysterectomy, and women who had been diagnosed with any bleeding disorder, including Von Willebrand disease.

After obtaining verbal consent, we directed up close and personal meetings with patients in the thrombosis clinic. We obtained information about age, marital status, use of contraception, and the length and planned duration of anticoagulation therapy. We also obtained information about their menstrual history before beginning anticoagulation. This information included duration, passage of clots, intermenstrual post-coital bleeding, and diagnosis of IDA. Any changes related to these factors were evaluated from that point

onward to decide if it was necessary to change to another anticoagulant, or to alter the administration of rivaroxaban; specifically, to discontinue the administration of the drug for more than two days. In addition, we evaluated if it was necessary to consult a gynecologist for their heavy periods. At that point, we requested that they fill in the Arabic PBAC (disclosed by a member of the research team) with their next three menstrual cycles. We gave each patient standardized sanitary pads. We sent updates by instant message, and telephone calls with the patients helped to guarantee adherence to recording menstrual bleeding.

During follow-up, 8 out of 49 patients did not return the charts. When we reached out to them to find out why, we found that five of them had achieved menopause during the study period; one had amenorrhea secondary to hormonal intrauterine contraceptive device (IUCD) insertion; and one had changed their anticoagulant medication to enoxaparin. In addition, we lost contact with one patient.

Primary Outcome Measures
Primary Outcome
The prevalence of heavy menstrual bleeding among women using rivaroxaban.

Secondary Outcome
The median of duration of menstruation, passage of clots, and diagnosis with IDA before and after the use of rivaroxaban.

The correlation between PBAC score and age, IDA.

RESULTS
49 patients were enrolled in the study and gave verbal consent. Baseline characteristics are shown in Table-1.

As from our pilot study on women not undergoing anticoagulant therapy, the median PBAC score was 72 IQR (37.5, 158.5), and 95th centile was 339. We defined heavy menstrual bleeding as any score above 339. The prevalence of heavy menstrual bleeding among women taking rivaroxaban is 22%. The median PBAC score for an average of 3 months was 211, IQR (42.5, 375.9). The menstrual history before and after starting rivaroxaban is shown in Table-2.

On multivariate correlations, we found a weak positive correlation between age and average PBAC score, as shown in Figure 1 and 2.

In using Spearman's correlation coefficient, there is a weak correlation between IDA and age, and IDA and average PBAC score, as shown in Figure-3.

Table-1: Baseline characteristics of patients

Median age	38 years IQR (30,43.5)
Marital status	(35,72%) married (10,20%) single (4,8.2%) divorced/widow
Indication of anticoagulation	(16,32.7%) DVT (11, 22.4 %) PE (6, 12.2 %) DVT and PE (14,28.6%) Thrombosis of unusual site (2,4.1%) Non-valvular AF
Duration of anticoagulation	(8, 16.3%) 1 month (3, 6.1%) 2 months (5, 10.2%) 3 months More than 3 months (33, 67.3%)
Intended duration of anticoagulation	(2, 4.2%) 3 months (3, 6.3%) 6 months (7, 14.6%) 1 year (36, 75%) lifelong
Contraception	94% Not using any contraception 4% Hormonal intrauterine device 2% Copper intrauterine device
Percentage of women needed to alter anticoagulation (discontinue for 2 or more days)	22%
Percentage of women needed to switch anticoagulation	2%
Percentage of women needed to consult gynecologist for heavy periods	12%

Table-2: Menstrual history before and after starting rivaroxaban

	Before starting rivaroxaban	After starting rivaroxaban
Median duration of menstruation	7 days IQR (5.5,7)	7 days IQR (6.5,9)
Percentage of women passing clots	21 (42.9%)	29 (59.2%)
Diagnosis of IDA	31 (63.3%)	27 (55.1%)
Intermenstrual bleeding	1 (2%)	7 (14.3%)
Post-coital bleeding	2 (5.1%)	2 (5.1%)

Figure: 1

Multivariate Correlations

	age	Average PBAC score	Presence of anemia after starting rivaroxaban
age	1.0000	0.0425	0.0878
Average PBAC score	0.0425	1.0000	0.2507
Presence of anemia after_ starting rivaroxaban	0.0878	0.2507	1.0000

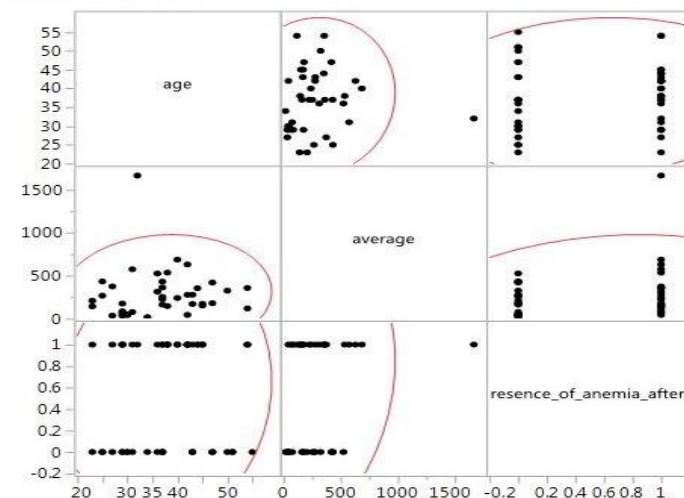There are 8 missing values.   The correlations are estimated by REML method.

Scatterplot Matrix

Figure: 2
Multivariate Correlations

	age	average
age	1.0000	0.0716
Average PBAC score	0.0716	1.0000

There are 8 missing values.   The correlations are estimated by REML method.
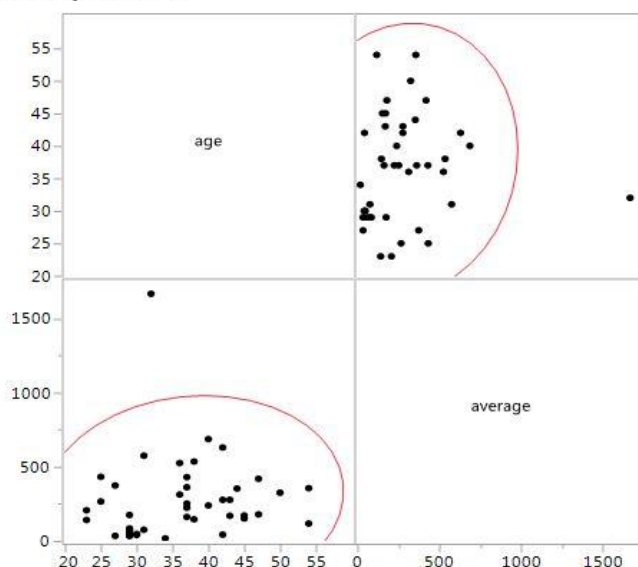
Scatterplot Matrix

Figure: 3

Nonparametric: Spearman's ρ

Variable	by Variable	Spearman ρ	Prob>|ρ|	
Average PBAC core	age	0.2354	0.1384	
Presence of anemia after_ starting rivaroxaban	age	0.1047	0.4742	
Presence of anemia after starting rivaroxaban	Average PBAC score	0.2398	0.1311	

LIMITATIONS

This is a prospective study, and therefore has various limitations. First, the number of patients selected was small. Second, not all patients returned the charts. Third, the history of menstrual cycle prior to initiation of rivaroxaban can be affected by recall bias. Fourth, a 3-month follow-up is too short of time to decide on the percentage of women who may need to switch to another anticoagulant. Finally, IDA was diagnosed less in women taking rivaroxaban, which may be explained by early diagnosis and treatment of IDA. These patients are on a routine follow-up for complete blood count with each clinic visit.

CONCLUSIONS

Rivaroxaban was associated with heavy menstrual bleeding in previous studies. In our prospective study, we found rivaroxaban was associated with a high prevalence of heavy menstrual bleeding, but not prolongation of menstruation. It is associated with an increase in intermenstrual bleeding and passage of clots. It also increases the need for anticoagulation therapy, and the need to consult a gynecologist for heavy periods. We recommend a detailed menstrual history for any women in reproductive age who require anticoagulation, and who report heavy periods to avoid rivaroxaban. We also recommend that the follow-up should include a complete blood count to evaluate for the presence of IDA. Another study with larger number of patients is required.

Conflict of interest: None

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