ORIGINAL ARTICLE

FREQUENCY OF MAJOR BLEEDING EPISODES WITH RIVAROXABAN FOR ATRIAL FIBRILLATION RELATED STROKE PREVENTION IN CHRONIC KIDNEY DISEASE PATIENTS

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Objectives: To determine frequency of bleeding complications with Rivaroxaban for Atrial Fibrillation in patients of chronic kidney disease (CKD).

Methodology: This Descriptive study was conducted on 280 patients fulfilling the inclusion criteria. After approval from Ethical Review Committee of Jinnah Hospital Lahore and informed consent, participants received tab. Rivaroxaban 20mg daily (Creatinine-Clearance >50mL/Min). Participants were followed for 4-weeks for any major bleeding complications. All information was collected on a questionnaire and results were calculated.

Results: In our study, Mean age of participants was 55±11 years with 59% males and 41% females. Mean duration of CKD calculated was 6±4 years. In this study major bleeding episodes occurred in 36 participants out of 280; 15 participants in age group up to 50 years and 21 participants in above 50 years developed it. It occurred in 20 males and 16 females; 5 cases in group with $CHADS_2VaSc$ score (annexure 2) up to 5 and 31 cases in those with score more than 5, no case occurred with less than 1 year duration of CKD while 4 cases with CKD in between 1 to 3 years and 32 cases with CKD more than 3 years developed major bleeding.

Conclusion: Major bleeding episodes occurred in a significant number of CKD patients with use of Rivaroxaban. This bleeding incidence had no association with age, sex and duration of CKD. Increased rates were associated with increased $CHADS_2VASc$ score especially for fall in Hb and microscopic hematuria.

Keywords: bleeding, rivaroxaban, chronic kidney disease, atrial fibrillation

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INTRODUCTION

One of the most common arrhythmia is atrial fibrillation and represents one-third of the arrhythmia-related hospital admissions in the developed countries.[1] It is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation without effective atrial contraction.[2] Atrial fibrillation (AF) is a common comorbidity with chronic kidney disease (CKD) (10-15%) while 30% of those with AF has CKD.[3]

Among patients of AF with moderate to high risk of stroke on anticoagulation, those with persistent AF have a higher risk of thromboembolism and worse survival compared with paroxysmal AF.[4] The risk of stroke is similar in patients with or without valvular disease.[5] Patients with concomitant AF and CKD, have significantly higher risk of thrombotic complications, particularly ischemic stroke with a concomitant higher bleeding risk, increasing proportionally to the grade of renal failure.[6] Renal impairment doubles the risk of stroke & increases the risk of major bleeding by almost 60% in anticoagulated patients with AF.[7] The presence of CKD amongst patients with AF was associated with an increase in risk for stroke or systemic embolism by 1.49-fold, myocardial infarction by 2-fold, major bleeding by 1.33-fold and all-cause mortality by 2.37-fold. Given the consistency of the association between CKD and AF, the guidelines include CKD as a risk factor for AF.[8]

New oral anticoagulants are now recommended for non-valvular AF as a potential alternative to Warfarin because less monitoring is required and no interaction with food it has a better compliance as well as safety profile.[9] The rates of stroke or systemic embolism of Rivaroxaban vs. Warfarin, were consistent among patients with moderate renal dysfunction, 2.32% Rivaroxaban vs. 2.77% Warfarin and patients without moderate kidney dysfunction i.e. $CrCl \geq 50$ ml/min; 1.57% and 2.00% respectively while on treatment.[10] In the older CKD population of more than 80 years, the risk of hemorrhage increases approximately 4-fold as compared with those aged younger than 66 years.[11] Longer time period is spent by CKD patients above

International Normalized Ratio (INR) target range. Moreover, despite frequent INR monitoring, had a higher INR variability compared with non-CKD patients.[12]

In a study published by Patel MR based on ROCKET AF trial showed major bleeding complications of 5.6% in group taking Rivaroxaban and 5.4% in those taking warfarin and 95% CI showed no difference in primary outcome in subgroups.[13] In another study, as compared to Warfarin Novel Oral Anticoagulants has a relative 50% risk reduction of intracranial hemorrhage and hemorrhagic stroke in elderly patients with non-valvular atrial fibrillation. Moreover, there is no need for frequent laboratory monitoring, no clear food or drug interactions and no need for dose adjustment.[14]

Rationale of this study was to determine bleeding complications with Non Vitamin-K antagonist in patient of chronic kidney disease as CKD is associated with more bleeding due to decreased platelet function and labile INR.

METHODOLOGY

Two hundred and eighty patients presenting at Jinnah Hospital Lahore Cardiology department, fulfilling the inclusion criteria were enrolled in this Descriptive study conducted from 1st May 2021 to 31st October 2021. After approval of synopsis from local Ethical Review Committee and informed written consent an ECG was done for each participant to document Atrial Fibrillation and detailed information about the patents' medical record and demographic history, including sex, age, $CHADS_2VASC$ and duration of disease was obtained. Then received tablets Rivaroxaban 20mg daily (CrCl >50mL/Min).

Subjects were explained the purpose of our study & followed up for 4-week period of time to see any major bleeding complications.

Participants were considered eligible if they were between 35-75 years, of either sex, presented to the hospital with Atrial Fibrillation determined on ECG (irregularly irregular rhythm) having $CHAD_2VASc$ score >2 and CKD (GFR 30-60ml). The patients who had CKD with atrial fibrillation with baseline INR > 2, chronic liver disease diagnosed on ultrasound (coarse liver) or liver function test (AST, ALT >40), Patient with contraindications to Rivaroxaban therapy, Valvular heart disease (Mitral stenosis & prosthetic valve ruled out by clinical history & Echo), Platelets <90,000 or Hb <10mg/dl, those not willing for study participation, GFR < 30ml/min, Pregnant, having Known bleeding disorders on medical record or with Recent Acute Coronary Syndrome were excluded from the study.

All the information was entered in a structured questionnaire and results were calculated. Data was analyzed in SPSS version 21.0. Means and standard deviations were calculated for quantitative variables like duration of CKD, age. Frequency and percentages were calculated for categorical variables like bleeding complications and gender. Data was stratified for gender, age, duration of disease and $CHADS_2VASC$. Post stratification chi-square test was used to assess the effect of those on outcome with $P \leq 0.05$ as statistical significance.

RESULTS

In our current study total 280 participants took part. The minimum age among the cases taking part in this study was 35 and maximum age was 75 with mean age 55±11. In this study 165 were male and 115 cases were female. The male to female ratio was 1.4. The mean duration of CKD in cases taking part was 6±4 years.

Table 1: Major bleeding episodes by age

Major Bleeding Episodes	Age		P-value
	Up to 50 years	Above 50 years	
Total bleedings	**15**	**21**	**0.585**
Organ	2 (13.3%)	2 (9.5%)	0.632
Falling Hb	4 (26.7%)	3 (14.3%)	0.431
Blood Transfusion	2 (13.3%)	3 (14.3%)	>0.999
Gross hematuria	2 (13.3%)	4 (19%)	>0.999
Microscopic hematuria	2 (13.3%)	2 (9.5%)	0.632
Melena	1 (6.7%)	2 (9.5%)	>0.999
Hematemesis	1 (6.7%)	3 (14.3%)	>0.999
Stool for occult blood	0 (0%)	1 (4.8%)	0.625
Intracerebral hemorrhage	1 (6.7%)	1 (4.8%)	0.610

In this study major bleeding episodes occurred in 36 (12.9%) and it did not occur in 244 (87.1%). Out of 36, organ bleed occurred in 4 (11.1%), Significant fall in Hemoglobin occurred in 7 (19.4%), blood transfusion was required in 5 (13.9%), Gross hematuria occurred in 6 (16.7%), Microscopic hematuria took place in 4 (11.1%), Melena in 3 (8.3%), Hematemesis developed in 4 (11.1%), Occult blood was found in 1 (2.8%) and intracerebral hemorrhage occurred in 2 (5.6%). Major bleeding episodes were stratified for gender, age, duration of CKD and $CHADS_2VASC$.

Table 2: Major bleeding episodes by gender

	Male	Female	P-value
Total (N)	**165**	**115**	**-**
Total bleeding	20 (12.1%)	16 (13.9%)	0.718
Organ	2 (10%)	2 (12.5%)	0.544
Falling Hb	3 (15%)	4 (25%)	0.451
Blood Transfusion	3 (15%)	2 (12.5%)	0.665
Gross Hematuria	5 (25%)	1 (6.25%)	0.406

Microscopic Hematuria	2 (10%)	2 (12.5%)	>0.999
Melena	2 (10%)	1 (6.25%)	>0.999
Hematemesis	2 (10%)	2 (12.5%)	>0.999
Occult Blood	1 (5%)	0 (0%)	0.589
Intracerebral hemorrhage	0 (0%)	2 (12.5%)	0.168

Table 3: Major bleeding episodes by $CHADS_2VASc$ score

	$CHADS_2VASc$		P-value
	> 5	≤ 5	
Total bleeding	31 (N)	5 (N)	0.031
Organ	4 (12.9%)	0 (0%)	>0.999
Falling Hb	5 (16.1%)	2 (40%)	0.048
Blood Transfusion	5 (16.1%)	0 (0%)	>0.999
Gross Hematuria	5 (16.1%)	1 (20%)	0.284
Microscopic Hematuria	2 (6.5%)	2 (40%)	0.015
Melena	3 (9.7%)	0 (0%)	>0.999
Hematemesis	4 (12.9%)	0 (0%)	>0.999
Occult Blood	1 (3.2%)	0 (0%)	>0.999
Intracerebral hemorrhage	2 (6.5%)	0 (0%)	0.896

Table 4: Major bleeding episodes by duration of chronic kidney disease (CKD)

	Duration of CKD			P-value
	≤1 year	1 to 3 years	>3 years	
Total bleeding	0	4	32	0.072
Organ	0 (0%)	0 (0%)	4 (12.5%)	0.495
Falling Hb	0 (0%)	1 (25%)	6 (18.75%)	0.417
Blood Transfusion	0 (0%)	0 (0%)	5 (15.63%)	0.219
Gross Hematuria	0 (0%)	0 (0%)	6 (18.75%)	0.177
Microscopic Hematuria	0 (0%)	1 (25%)	3 (9.38%)	0.807
Melena	0 (0%)	0 (0%)	3 (9.38%)	0.343
Hematemesis	0 (0%)	1 (25%)	3 (9.38%)	0.807
Occult Blood	0 (0%)	1 (25%)	0 (0%)	0.249
Intracerebral hemorrhage	0 (0%)	0 (0%)	2 (6.25%)	0.439

DISCUSSION

Clinicians should consider the effects occurred due to AF in renal disease patients very carefully, because it increases risk of medical complications related death.[8] For example, the incidence of stroke is significantly higher in all stages of CKD along with AF.[15]

In a Cochrane review of patients with CKD and non-valvular AF enrolled in phase 3 trials of DOACs (12,155 with stage 3 CKD and 390 with stage 4), subjects treated with DOACs compared to subjects receiving warfarin had a lower risk of stroke/systemic embolism (RR: 0.81) and a tendency to have fewer major bleeding episodes (RR: 0.79).[16]

However, the data published about the safety of anticoagulation therapy in concomitant AF and Renal Disease has been conflicting. Past studies have shown that patients with end-stage renal disease, have higher bleeding complications rate with anticoagulation therapy.[8]

In our study there was no statistically significant effect on bleeding episodes with increasing duration of CKD or with increasing stage of disease.

According to ROCKET-AF Trial on Rivaroxaban, clinically relevant minor and major bleeding episodes were 14.9% per 100 patient-years, Significant drop in Hb was 2.77%, Transfusion needed in 1.65%, organ bleed was seen in 0.82%, Intracranial hemorrhage (per 100 patient-years) was 0.5%, Fatal bleeding (per 100 patient-years) was 0.2%, major bleeding through Gastrointestinal system occurred in 3.2% per 100 patient-years for Rivaroxaban.

However in our study major bleeding occurred in 12.9%, organ bleed occurred in 4 (11.1%), Significant fall in Hemoglobin occurred in 7 (19.4%), blood transfusion was required in 5 (13.9%), Gross hematuria occurred in 6 (16.7%), Microscopic hematuria took place in 4 (11.1%), melena in 3 (8.3%), Hematemesis developed in 4 (11.1%), occult blood was found in 1 (2.8%) and intracerebral hemorrhage occurred in 2 (5.6%)

In a study, Compared with warfarin use, the use of rivaroxaban or apixaban was significantly associated with reduced risks of all-cause death (HR = 0.82, 95% CI 0.72-0.93) and gastrointestinal bleeding (HR = 0.87, 95% CI 0.80-0.95).[17]

In another study done by Coleman CI et al. 2017, outcomes for patients with AF and moderate-to-severe CKD on warfarin or Rivaroxaban (with similar demographics, comorbidities, risk factors for stroke, bleeding risk factors and medications) also showed no significant difference in rates of thromboembolism or major bleeding.[18]

Another study done in 2014 by Halperin and colleagues showed the use of Rivaroxaban in elderly patients. Patients were analyzed in 2 groups based on age <75 years or age ≥75 years at the start of study. It showed significantly more bleeding (4.63% vs. 2.74%/100 patient-years; $p < 0.0001$) compared with younger patients.[19]

A meta-analysis by Zou et al., showed that DOACs caused a similar decrease in risk of stroke/systemic embolism in normal kidney function participants as compared to warfarin (relative risk [RR]: 0.93). However, a reduction in risk was significantly more in cases of mild CKD (stage 2) (RR: 0.79) and moderate CKD (stage 3) (RR: 0.87). The decrease in major bleeding in those patients treated with DOACs was greater with warfarin both in normal kidney function and CKD.[20]

In another study by Patel MR et al., major bleeding risks in cases with renal disease & without renal disease were studied. Renal Disease patients had a higher rate of major bleeding than those not having renal disease, 4.52 per 100 person-years versus 2.54 per 100 person-years, respectively.[21]

A Lin YC et al. study compared the effect of Warfarin vs. Rivaroxaban in CKD patients for stroke prevention and results showed that cumulative incidence of major bleeding was similar between the 2 groups except gastrointestinal bleeding risk was lower in the Rivaroxaban group.[22]

According to results of our present study there was no association between age, sex or duration of disease with the incidence of bleeding with Rivaroxaban. Moreover, no statistically significant episode of bleeding seen with use of Rivaroxaban in CKD patients for Atrial Fibrillation related stroke prevention.

There are no randomized trials of the efficacy and safety of DOACs and VKA in advanced CKD. On the other hand, observational studies suggest that DOACs, compared to warfarin, are associated with a lower risk of acute kidney damage and generation/progression of CKD.[23]

But the current study has limitations as it is studied on a small subset of sample, in just one hospital setting with limited resources. So this study needs further workup in a bigger set up to elaborate bleeding risks in CKD patients. The loops and wholes of this study can only be filled by further research work in future.

CONCLUSION

This study concluded that major bleeding episodes occurred in a significant number of CKD patients with use of Rivaroxaban. This bleeding incidence had no association with age, sex and duration of CKD. Increased rates were associated with increased CHADS2VASc score especially for fall in Hb and microscopic hematuria.

According to our study, use of Rivaroxaban in CKD patients for atrial fibrillation related stroke prevention has more chances of bleeding. However, further research and randomized controlled trials are required to further strengthen the evidence.

AUTHORS' CONTRIBUTION:

ST: Concept and design, data acquisition, interpretation, drafting, critical revision, final approval, and agree to be accountable for all aspects of work. NI, MBT, IS, SS, OS: Data acquisition, interpretation, drafting, critical revision, final approval, and agree to be accountable for all aspects of work.

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