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Apixaban vs Warfarin: Safety In Patients with Advanced Kidney Disease

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ABSTRACT

Objective: To compare the safety of Apixaban and Warfarin in patients suffering from advanced chronic kidney disease

Study Design: Comparative Cross-sectional study

Place and Duration of Study: Department of Medicine and Nephrology Pak Emirates Military Hospital Rawalpindi, Pakistan from Aug 2021 to Jul 2022.

Methodology: A total of 135 cases of advanced chronic kidney disease (stage IV and V) requiring anticoagulation for deep venous thrombosis or atrial fibrillation were recruited in the study. They were randomly divided into two groups. Patients in group I received Apixaban while patients in group II received Warfarin for anticoagulation. They were followed up for three months to look for safety. Major bleeding, Fatal bleeding, non-fatal major bleeding at a critical site and other non-fatal bleedings were compared in both the groups for three months of treatment with the assigned medication.

Results: Out of 135 patients of advanced chronic kidney disease managed for atrial fibrillation or deep venous thrombosis, 70(55.6%) patients were males and 55(44.4%) were females. 66(48.9%) took Apixaban while 69(51.1%) took Warfarin for anticoagulation. Bleeding related adverse effects like major bleeding, fatal bleeding, non-fatal major bleeding at a critical site and other non-fatal bleedings were not statistically significant in both the groups (p-value>0.05).

Conclusion: Both medications were relatively safe and rate of different types of bleeding was quite low in both the groups. Both medications turned out to be not very different in terms of safety profile in patients suffering from advanced chronic kidney disease.

Keywords: Apixaban; Chronic kidney disease; Safety; Warfarin

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INTRODUCTION

Statistics across the globe show that chronic kidney disease has been major cause of mortality and morbidity among individuals of almost all age groups.[1] Both developed and developing countries bear the burden of chronic renal disease and it has a huge impact on health care budget.[2,3] Treatment options for this chronic and debilitating disease vary according to condition of patients and expertise available.[4] Prolong chronic renal failure even if treated may result in multisystem problems requiring a multidisciplinary approach from treating team.

Hematological and biochemical abnormalities are found in all stages of chronic kidney disease and usually increase as the disease advances.[5] Complications of these abnormalities include atrial fibrillation and deep venous thrombosis. Considerable number of patients suffer from these problems during the course of CKD and need anticoagulation in one way or other.[6] Treating team has to consider number of factors before starting the patient on anticoagulation and making choice of agent used for this purpose.

As advanced CKD may sometime be associated with pro-thrombotic conditions so number of studied have been done in past regarding safety and efficacy of anticoagulants in these patients. Chokesuwattanaskul et al. in 2018 published a meta-analysis of five studies comparing Warfarin and Apixaban in patients of end stage kidney disease.[7] Meta-analysis concluded that Apixaban was slightly more effective and safe as compared to Warfarin. Safety was measured in terms of major bleeding in the patients. Hanni et al. in 2020 published a study with an objective to assess outcomes with Warfarin and Apixaban used for anticoagulation in patients of chronic renal disease. They revealed that overall there was not much gross difference in adverse effect profile but Apixaban was slightly more safe so could be used as an alternative to warfarin.[8] Patients of CKD with atrial fibrillation were studies for difference in safety profile of Apixaban and Warfarin. They came up with the findings that Apixaban cause less bleeding events as compared to Warfarin.[9]

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Health budget of Pakistan is limited and resources need to be tailored by the clinicians. Newer and expensive agents are used if efficacy is safety is proven to be superior in local population. A recent local study published by Tahir et al. in 2022 regarding safety of Rivaroxaban in patients of CKD for atrial fibrillation related stroke prevention. They concluded that considerable number of patients had bleeding episodes in their data set.[10] Limited local data has been generated regarding comparison of various anticoagulation agents used in CKD patients in terms of bleeding episodes. We planned this study with a rationale to compare the safety of Apixaban and Warfarin in patients suffering from advanced chronic kidney disease managed at our hospital.

METHODOLOGY

This comparative cross-sectional study was conducted at departments of medicine and nephrology in Pak Emirate Military Hospital Rawalpindi from August 2021 to July 2022. Sample size was calculated by WHO Sample Size Calculator with population prevalence proportion of bleeding vents in patients on anticoagulation in CKD patients as 9.9%.[11] Non probability Consecutive sampling technique was used to gather the sample.

Inclusion Criteria: All patients of chronic renal disease stage four or five who were either dialysis dependent or non-dependent between the age of 18 and 65 were included in the study. Diagnosis and staging of Chronic kidney disease were done as per National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2012.[12]

Exclusion Criteria: Patients with any diagnosed clotting or bleeding disorders or using anticoagulants before onset of CKD due to any reason were excluded. Patients who refused to undergo study and wanted a specific agent were not recruited from the start. Patients with known allergies with any of the agents used in the study were excluded as well. Those who were using any other medications which could interfere with clotting or bleeding profile of the individual were also not included.

Ethical review board committee of the hospital was approached to get the ethical approval for this study via letter no A/28/EC/352/2021. Written informed consent was taken from all the potential participants of this study before enrolling them for study. Advanced chronic kidney disease (stage IV and V) requiring anticoagulation for deep venous thrombosis or atrial fibrillation were included in the study. They were randomly divided into two groups via lottery method. One group received Apixaban for anticoagulation in a dose of 5mg twice daily,[13] while group B received Warfarin in standard dose with target INR of 2.0-3.0.[14] Both the groups were followed up routinely in outpatient department for three months and adverse effects especially related to any bleeding event were noted by research team on a separate proforma. Team members who noted the adverse effects were not aware of the medication patients were using for anticoagulation. Adverse effects related to bleeding were categorized as major bleeding, fatal bleeding, non-fatal major bleeding at a critical site and other non-fatal bleedings. Major bleeding was defined in accordance with the definition provided by the International Society on Thrombosis and Haemostasis as bleeding causing a fall in hemoglobin level of $\geqslant$2 g/dL or leading to transfusion of $\geqslant$2 units of packed red blood cells. Bleeding in a critical area or organ included the following types of bleeding i.e intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome.[8,9]

Characteristics of participants were described by using the descriptive statistics. Chi-square and Fischer exact test were applied to look for the statistically significant difference for major bleeding, fatal bleeding, non-fatal major bleeding at a critical site and other non-fatal bleedings in the two study groups. All statistical analysis was performed using Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Differences between groups were considered significant if *p*-values were less than or equal to 0.05.

RESULTS

After application of criteria laid down for this comparative-cross-sectional analysis, one hundred and thirty-five patients were recruited. Out of 135 patients of advanced chronic kidney disease managed for atrial fibrillation or deep venous thrombosis, 70(55.6%) patients were males and 55(44.4%) were females. Table-I summarized the general characteristics of patients of advanced CKD requiring anticoagulation. 66(48.9%) took Apixaban while 69(51.1%) took Warfarin for anticoagulation. 40(29.6%) patients had grade IV CKD while 95(70.4%) were suffering from grade V CKD. Out of all the study participants, 58 (42.9%) were haemodialysis dependent while 77(57.1%) were non-dialysis dependent.

Regarding bleeding related adverse effects it was observed that 11(8.1%) had major bleeding, 2(1.4%)

had fatal bleeding, 4(2.8%) had non-fatal bleeding of critical site while 7(5.1%) had other non-fatal bleeding. Results of statistical analysis have been shown in Table-II. Bleeding related adverse effects like major bleeding (*p*-value-0.383), fatal bleeding (*p*-value-0.975), non-fatal major bleeding at a critical site (*p*-value-0.964) and other non-fatal bleedings (*p*-value-0.261) we're not statistically significant in both the groups.

Table-I: Characteristics of Study Participants

Study parameters	n (%)
Age (years) Mean + SD Range (min-max)	49.63 ±5.59 years 23 years-60 years
Gender	
Male	75(55.6%)
Female	60(44.4%)
Type of agent used	
Apixaban	66(48.8%)
Warfarin	69(51.2%)
Grade of Chronic Kidney disease	
IV	40(29.6%)
V	95(70.4%)
Dialysis Dependent	
No	58(42.9%)
Yes	77(57.1%)
Bleeding related adverse effects	
Major bleeding Fatal bleeding Non-fatal bleeding of critical site Other non-fatal bleeding	11 (8.1%) 2 (1.4%) 4 (2.8%) 7 (5.1%)

Table II: Comparison of Bleeding Related Adverse Effects In Both the Groups

Adverse effects	Apixaban	Warfarin	*p*-value
Major bleeding			
No	6(93.9%)	62(89.8%)	0.383
Yes	04(6.1%)	07(10.2%)	
Fatal bleeding			
No	65(98.4%)	68(98.5%)	0.975
Yes	01(1.6%)	01(1.5%)	
Non-fatal bleeding at critical site			
No	64(96.9%)	67(97.1%)	0.964
Yes	02(3.1%)	02(2.9%)	
Other non-fatal bleeding			
Within limit	64(96.9%)	64(92.7%)	0.261
Deranged	02(3.1%)	05(7.3%)	

DISCUSSION

Apixaban and Warfarin did not differ significantly in terms of safety profile in our study participants. Chronic kidney disease especially in advanced stages prone the patient towards number of multi-system complications. Adverse effects of medications also get more marked in this compromised state of body. Medications used for anticoagulation always carry the risk of bleeding and it becomes more in cases where body is already having marked hematological and biochemical disturbances. Apixaban is a relatively new but expensive agent used widely for anticoagulation in recent times. Being from a developing country, we need to know that is it really proving any added benefit in terms of efficacy and safety as compared to cost effective agents like Warfarin. We therefore conducted this study with an aim to compare the safety of Apixaban and Warfarin in patients suffering from advanced chronic kidney disease managed at our hospital.

Fu *et al.*, in 2021did a comparison between Apixaban and Warfarin in CKD patients suffering from atrial fibrillation. They came up with the findings that Apixaban was associated with less risk of stroke, systemic embolism and major bleeding when compared to Warfarin.[15] Our results were different from them as all types of bleeding events studied were not statistically significantly different in patients taking Apixaban or Warfarin.

A study conducted in United States in 2020 compared safety profile of Warfarin and Apixaban in patients suffering from moderate to severe CKD.[16] They concluded that major bleeding rates were not different in both the groups but minor and composite bleeding rates were higher in patients taking Warfarin. Our results showed that both medications were relatively safe and rate of different types of bleeding was quite low in both the groups. Both medications turned out to be not very different in terms of safety profile in patients suffering from advanced chronic kidney disease.

Starr et al. published a review in 2022 regarding use of anticoagulants in patients with stage V chronic kidney disease and those managed with hemodialysis. They stated that Apixaban or Rivaroxaban were safe choices as was Warfarin and clinicians can use any of them if there is a requirement of anticoagulation in these patients.[17] Our results were similar as there were no significant difference in bleeding rates in patients taking Apixaban and Warfarin.

A database of around 29,790 CKD patients was evaluated by Cohen *et al.* regarding efficacy and safety of Apixaban and Warfarin. They revealed that major bleeding was seen less in patients who took Apixaban as compared to those who took Warfarin.[18] Our study

showed slightly different results as all types of major, fatal and non-fatal bleeding events did not differ significantly between the patients taking Warfarin or Apixaban.

LIMITATION OF STUDY

Safety parameters were only looked for three months therefore long term safety could not be established in our study. A Number of biochemical and hematological factors make the patients prone towards bleeding in patients of chronic kidney disease therefore it cannot be concluded with this study design that bleeding related complications were exactly due to the anticoagulant agent used in the patient.

CONCLUSION

Both medications were relatively safe and rate of different types of bleeding was quite low in both the groups. Both medications turned out to be not very different in terms of safety profile in patients suffering from advanced chronic kidney disease.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AT: & KM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

MH: & FZ: Data acquisition, data analysis, approval of the final version to be published.

SAT: & AA: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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