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ORIGINAL ARTICLE

Safety and Effectiveness of Direct Xa Inhibitors vs Warfarin in Patients with Nephrotic Syndrome

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ABSTRACT

Introduction: Nephrotic syndrome (NS) is characterized by excessive proteinuria (> 3.5 g/day), hypoalbuminemia, and edema.
Objectives: The main objective of the study is to find the safety and effectiveness of direct Xa inhibitors vs warfarin in patients with nephrotic syndrome.
Material and methods: This cross-sectional study was conducted in Akbar Niazi Teaching Hospital, Barakahu, Islamabad from January 2022 till June 2022. The data were collected from 120 patients which diagnosed with nephrotic syndrome. After permission from hospital ethical committee, total 120 patients meeting the inclusion and exclusion criteria was enrolled in the study. Detailed history of kidney disease and physical examination was done to meet the inclusion and exclusion criteria. Informed consent was obtained.
Results: The data was collected from 120 patients. Out of 120 participants, 60 were treated with warfarin while 60 were considered as control group. Median age was 26 years in group I and 25.3 years in group II (p=0.705). Female cases counted for 41 (86%) and 19 (14%) in I and II groups, respectively. Risk factors, clinical presentation, affected vessels and AF for both groups are depicted in Table I. Results from both groups were comparable and statistically, no significant differences were observed (p• value more than 0.05). Practical implication: This study will help in treating nephrotic syndrome and kidney complications.
Conclusion: It is concluded that awareness about nephrotic syndrome in patients were low and its prevalence continues to remain high and is likely to increase globally. Direct Xa inhibitors were associated with lower hazards of kidney complications and mortality than warfarin in patients with nephrotic syndrome.
Keywords: Nephrotic, Syndrome, Complications, Mortality, Warfarin

INTRODUCTION

Nephrotic syndrome (NS) is characterized by excessive proteinuria (> 3.5 g/day), hypoalbuminemia, and edema. It is associated with a variety of different glomerular pathologies, including membranous glomerulonephritis, focal and segmental glomerulosclerosis, minimal change disease, and IgA nephropathy[1]. The glomerular filtration barrier defect in NS leads to urinary loss of natural anticoagulants and other plasma proteins, which stimulates hepatic protein synthesis, including the synthesis of coagulation-related proteins[2]. These changes cause a hypercoagulable state with an up to 25% increased risk of TE that may be even further increased in patients with membranous glomerulonephritis. Deep vein thrombosis and pulmonary embolism has overall been associated with a 6% and 12% 30-day mortality, respectively, but have never been evaluated in NS patients[3].

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults and is associated with an increased risk of thromboembolic stroke; therefore, anticoagulation is the cornerstone of its management[4]. Patients with AF who have severe chronic kidney disease (CKD) requiring dialysis have significantly higher incidence rates of ischemic stroke. In addition, there is a higher incidence of AF among patients who have end-stage renal disease (ESRD), with an increased incidence of bleeding and complications[5]. For decades, warfarin has been the cornerstone of anticoagulation in patients with AF. However, the safety of warfarin in patients on dialysis is questioned as it may cause a higher incidence of bleeding. Additionally, the efficacy of warfarin in stroke prevention among patients with AF who are on dialysis is debatable[6]. Direct oral anticoagulant agents (DOACs) have been proved to have comparative efficacy and safety profiles as warfarin in reducing the risk of thromboembolic stroke and they are currently widely used in many patient groups. DOACs have been shown to be non-inferior to warfarin in mild to moderate CKD[7].

Warfarin is a vitamin K antagonist (VKA) that has been used in the prevention of AF for over 50 years. Randomised trials have shown that warfarin is superior to placebo, aspirin and the combination of aspirin–clopidogrel in preventing stroke. Warfarin use is challenging due to its narrow therapeutic index and it has many food and drug interactions. The number of patients with atrial fibrillation (AF) who need stroke prevention continues to rise[2]. The hypercoagulability in NS is not fully understood but has been ascribed to at least three different mechanisms. First, elevated thromboxane A2 may increase platelet activation and aggregation[8]. Second, urinary loss of natural anticoagulants such as antithrombin and protein S combined with increased hepatic synthesis of fibrinogen and coagulation factor V and VIII results in a prothrombotic state. Finally, decreased plasmin levels due to urinary loss, in combination with increased plasminogen activator inhibitor-1 levels, result in decreased fibrinolytic activity[9]. Given this lack of knowledge, international guidelines recommend prophylactic anticoagulation for patients with severe NS defined by the underlying condition and serum-albumin. Thus, prophylactic anticoagulation is recommended to patient with plasma-albumin below 24 g/L if membranous nephropathy and below 20 g/L in other conditions[10]. The introduction of direct oral anticoagulants (DOACs), including direct inhibitors of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban), has changed the landscape of VTE treatment. Based on several landmark randomised controlled trials (RCTs),8–11 the 2014 European Society of Cardiology Guidelines on acute PE suggested that rivaroxaban, apixaban or dabigatran should be considered as an alternative to vitamin K antagonist (VKA) during extended oral anticoagulation (OAC) therapy[11].

Objectives: The main objective of the study is to find the safety and effectiveness of direct Xa inhibitors vs warfarin in patients with nephrotic syndrome.

MATERIAL AND METHODS

This cross-sectional study was conducted in Akbar Niazi Teaching Hospital, Barakahu, Islamabad from January 2022 till June 2022. The data were collected from 120 patients which diagnosed with nephrotic syndrome.

Inclusion Criteria:

- Age between 18 to 60 years.
- Both male and female.
- Patients diagnosed with nephrotic syndrome.

Exclusion criteria:

- Already taking any anticoagulant drug
- Any bleeding disorder.
- Patients who are not willing to give consent

Data Collection: After permission from hospital ethical committee, total 120 patients meeting the inclusion and exclusion criteria was enrolled in the study. Detailed history of kidney disease and physical examination was done to meet the inclusion and exclusion criteria. Informed consent was obtained.

The data was collected into two groups:

Group I: Treated with Warfarin

Group II: treated with Xa factor (Rivaroxaban)

Group I patients were treated with warfarin 15mg daily twice a day for one month then 20mg daily for 5 months throughout the treatment period and Group II patients with rivaroxaban 15mg daily twice a day for one month then 20mg daily for 5 months. Diagnosis was made with a clinical presentation of nephrotic syndrome. Both the groups were followed during hospitalization and after the discharge of the patient for 30 days for the development of any complications. Effectiveness was defined as ischemic stroke or systemic embolism. Safety was defined as intracranial hemorrhage or gastrointestinal bleeding. Post-discharge follow up was done monthly on an OPD basis.

Statistical Analysis: All the data were analyzed by SPSS (Statistical Package for social sciences release 20.0; SPSS, Inc; Chicago, IL) system for Windows. Continuous variables are expressed as mean ± SD (Standard deviation) while categorical variables are expressed as frequencies and percentages.

RESULTS

The data was collected from 120 patients. Out of 120 participants, 60 were treated with warfarin while 60 were considered as control group. Median age was 26 years in group I and 25.3 years in group II (p=0.705). Female cases counted for 41 (86%) and 19 (14%) in I and II groups, respectively. Risk factors, clinical presentation, affected vessels and AF for both groups are depicted in Table I. Results from both groups were comparable and statistically, no significant differences were observed (p• value more than 0.05).

Table 1: Demographic characteristics of selected patients

Baseline characteristics	All patients	Warfarin	Rivaroxaban	p-Value
AGE (mean, min-max)	25.3 (15–45)	26 (15–36)	27 (15–45)	
GENDER				
Male	13 (18%)	14 (14%)	15 (21%)	
Female	47 (82%)	46 (86%)	45 (79%)	
RISK FACTOR				
OCP	08 (18%)	03 (14%)	05 (21%)	.613
Anemia	13 (29%)	06 (29%)	07 (29%)	
Dehydration	06 (13%)	04 (19%)	02 (08%)	
Pregnancy/Puerpureum	22 (49%)	10 (48%)	12 (50%)	
Unknown Factor	07 (16%)	03 (14%)	04 (17%)	
Thrombophilia	04 (09%)	01 (05%)	03 (13%)	
Ischemic stroke	25 (56%)	12 (57%)	13 (54%)	.843
Hemorrhagic stroke	17 (38%)	08 (38%)	09 (38%)	.968
Myocardial infarction	13 (29%)	06 (29%)	07 (29%)	.965
Intracranial hemorrhage	17 (38%)	08 (38%)	09 (38%)	.968
Duration (months) mean (min-max)	03 (03–12)	03 (03–12)	03 (03–12)	.058

Blood pressure, blood urea nitrogen, serum creatinine and urine specific gravity were presented in table 02. Patients with nephrotic syndrome had significantly lower hemoglobin, and higher reticulocyte counts, CRP and inflammation also present in patients.

Table 2: Laboratory investigation of Selected Patients

Parameter	Mean ± SEM	Range/%
Hemoglobin (g/dL)	9.2 ± 0.12	7.0–13
Reticulocyte %	9.2 ± 0.57	2.4–24.7
C-reactive protein (mg/L)	2.4 ± 0.73	0.3–28.4
Blood pressure (Systolic)	113 ± 1.4	96–157
Blood pressure (Diastolic)	63.6 ± 0.92	46–96
Urine albumin (mg/g creatinine)	132.4 ± 60.3	11.33–5145
Urine Sp. Gravity	1.011 ± 0.0003	1.0–1.03
Blood urea nitrogen (mg/dL)	23.45 ± 0.57	4–36
Serum creatinine (mg/dL)	2.78 ± 0.03	0.3–1.4

The P-value of the gender male was 0.027 and female was 0.159. Female showed more positive results than male in both Group A and group B. The number of patients in both groups were 55.

Table 3: Stratification of drug efficacy with respect to gender.

Gender	Group A (n=60) Efficacy		Group B (n=60) Efficacy		P-value
	Yes	no	yes	No	
Male	22	04	15	11	0.027
Female	26	08	22	12	0.159

DISCUSSION

Previous research has shown that the risk of TE in NS patients varies significantly depending on the degree of the diagnostic screening and the underlying disease, with the highest risk in patients with membranous glomerulonephritis. In a cohort study including 206 NS patients not receiving prophylactic anticoagulation the overall incidence of TE was 6.8%[11]. These patients had a serum albumin level below 19 g/L with different types of pathological leading to NS. We have previously reported an incidence of TE of 12% in a cohort of 35 NS patients also not receiving thromboprophylaxis and with a plasma albumin ranging from 11–29[12]. In the cohort, on which the GN-risk-score is based, the frequency of TE in NS due to membranous glomerulonephritis and a serum albumin < 20 g/L was 11%. Based on these data, we estimate that the expected incidence of TE in this case series would be between 0.2 and 1.3 patient cases if not receiving prophylactic anticoagulation[13].

To our knowledge, only two case reports have been published on patients receiving DOAC as thromboprophylaxis in NS[14]. Sexton et. al. reported two patients with membranous glomerulonephritis and minimal change disease, respectively, prescribed apixaban as thromboprophylaxis[15]. No TE was observed, while one patient had an episode of epistaxis, during treatment. Basu et al. described a patient with systemic lupus erythematosus related NS and treatment failure on both VKA, LMWH and rivaroxaban[16]. It was suggested that variations in plasma coagulation factors associated with NS may have rendered anticoagulant treatment ineffective[17].

CONCLUSION

It is concluded that awareness about nephrotic syndrome in patients were low and its prevalence continues to remain high and is likely to increase globally. Direct Xa inhibitors were associated with lower hazards of kidney complications and mortality than warfarin in patients with nephrotic syndrome. Although the use of these agents in NS likely requires further study before widespread adoption, the experience to date, although limited, appears promising.

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