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Original Research Article

Evaluation of Acute Kidney Injury Brought on by Warfarin Anticoagulation and Haematuria

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Abstract

Introduction: According to reports, glomerular haemorrhage can cause warfarin-related nephropathy to develop at an INR of 2.0. Prospective studies evaluating the impact of supratherapeutic warfarin anticoagulation on haematuria and acute renal damage are lacking (AKI). Due to their older age, higher rates of kidney disease, and other concomitant conditions, older people may be more vulnerable. The purpose of this study was to ascertain the prevalence and type of haematuria and AKI in older individuals on warfarin, as well as any correlations with elevated INR values.

Method: This study involved 100 patients who were acutely hospitalised at a tertiary hospital and were using the anticoagulant warfarin. RIFLE criteria were used to evaluate AKI. Urinalysis was carried out to determine the amount of haematuria, describe the erythrocyte shape, and gauge the albumin-creatinine ratio. Following up on positive cases for 3-5 weeks to ascertain resolution.

Result: In 53% of patients, an INR 2.0 was discovered. The risk of excessive anticoagulation increased with pre-admission antibiotic treatment. AKI, haematuria, and both had isolated incidences of 18.6, 13.2, and 11%, respectively. An INR of 3.0, non-urinary infection, catheterization, and albuminuria were all risk factors for haematuria. The majority of AKI patients were moderate, and there was no conclusive link between admission INR and AKI. An increased risk of persistent renal impairment at follow-up was strongly related with admission with heart failure.

Conclusion: A higher incidence of haematuria, but not AKI, was linked to supratherapeutic warfarin anticoagulation. The majority of haematuria instances were temporary.

Keywords: Warfarin Anticoagulation, Acute Kidney Injury, Haematuria, Warfarin, Nephropathy.

Introduction

A recently identified condition known as "warfarin-related nephropathy" (WRN) is characterised by an abrupt increase in blood creatinine and excessive anticoagulation (INR[3.0). Red blood cell (RBC) casts and tubular damage were found in the renal biopsies of individuals with macroscopic haematuria brought on by over-anticoagulation with warfarin [1]. This suggests that RBCs are obstructing the tubules. Patients who have IgA nephropathy and macroscopic haematuria may experience the condition, which has similarities to acute kidney injury (AKI) [2]. Iron, haemoglobin, or other compounds released from RBCs could also cause direct tubular poisoning. The histopathology of a rat model of WRN has been described, and it shows glomerular haemorrhage, obstructive RBC casts, tubular damage, and glomerular endothelial cell death [3]. Vitamin K administration to rats may provide protection from this harm [4].

Increased mortality [6,] confounding of nephrology studies [7], and the progression of chronic kidney disease (CKD) have all been linked to excessive anticoagulation. WRN is twice as common in the CKD group compared to the non-CKD population, with an estimated prevalence of 20% [6]. Patients with CKD may be more likely to over-anticoagulant because they spent less time within the target range, needed modifications more frequently, and had a higher risk of bleeding [8, 9]. These findings might help to explain why CKD patients have a higher incidence of WRN. Retrospective research can only be interpreted so far because of variables like concomitant sickness and medication use. There aren't any prospective investigations of WRN, hence the diagnosis is merely speculative. Dipstick urinalysis was employed in earlier investigations, however there is no information on RBC morphology. Dysmorphic RBCs should be seen and could serve as a valuable sign of WRN as a probable cause of AK if glomerular haemorrhage is the pathophysiology of WRN.

In acutely sick patients undergoing warfarin medication, we aimed to ascertain the link between haematuria and AKI and a supratherapeutic INR. Given the high rate of warfarin usage and the frequency of CKD, we concentrated on elderly patients as a vulnerable category. Additionally, we looked into the link between albuminuria and short-term outcomes and RBC shape.

Methods

Patients and study design

At Patna Medical College, Patna, Bihar, we carried out a 6-month prospective observational research. More than 200 non-elective patients were admitted to the general medicine unit during this time, and 11% of them were given warfarin. Patients who were admitted for at least one night were qualified. The following conditions were excluded: dialysis, terminal care, long-term catheterization, urinary tract infection, and readmission lasting less than 28 days. Patients who were eligible were found using the computerised admittance. Pre-admission INR, demographic information, and medication use (including antibiotic use in the previous three weeks) were all tracked. INRs were checked every day till release.

The creatinine test

Jaffe assays with traceable calibration for standard isotope-dilution mass spectrometry (IDMS) were used to quantify creatinine. According to the Australasian Creatinine Consensus Working Group [10], estimated glomerular filtration rates (eGFR) values were calculated using the Modification of Diet in Renal Disease (MDRD) equation.

Results and follow-up of the study

The RIFLE criteria were used to define AKI [11]. The best laboratory finding from the previous five to twelve months was used to determine baseline renal function. Blood pressure and urine production were monitored for 47 hours. A clinician evaluation assessed whether hypovolaemia was present. A renal scan was performed on oliguric patients to rule out blockage. Within 47 hours of admission, a midstream urine sample was taken for analysis by RBC count, phase contrast microscopy, culture, and albumin-creatinine ratio (ACR). The morphology of the RBCs in urine was categorised as glomerular, non-glomerular, or undetermined. There are three levels of hemoturia: light, moderate, and heavy. ACR was divided into three categories: macroalbuminuria, microalbuminuria, and normal. Patients who had AKI or haematuria were reassessed three to five weeks later.

Statistical Analysis

SPSS version 19 was used to conduct the analysis. A P< 0.04 was regarded as statistically significant when data were presented as mean standard deviation. The Pearson's correlation coefficient was used to determine the correlation between continuous variables (r). The link between categorical variables was examined using the Chi-square test for independence. For continuous variables, differences in mean values were assessed using an unpaired t test. To investigate a number of predictor variables for the outcome of AKI, logistic regression was performed. The predictive usefulness of an INR value for haematuria and AKI was assessed using a receiver operating curve (ROC) and area under the curve (AUC).

Results

Patient characteristics

There were 120 patients who qualified**.**

Table 1: Displays the baseline traits.

Characteristics	**No. of Patients**
Age	81±7
Gender (female)	26 (37%)
Anticoagulation	
Admission	3.6±2.1
Pre-admission	2.5 ± 0.5
INR testing gap (days)	9.8 ± 9.4
Patients with INR	80 (53%)
Duration INR	2.1 ± 0.7
Discharge	
Kidney Function	
Normal	13 (9.2%)
Stage 2	52 (36.6%)
Stage 3a	35 (23.2%)
Stage 3b	32 (22.1%)
Stage 4	12 (8.6%)
Combordities	
Diabetes mellitus	35 (24.1%)
Ischaemic heart disease	62 (42.1%)
Heart failure or cardiomyopathy	71 (48.1%)
Hyperlipidaemia	66 (44.6%)
Hypertension	91 (66.6%)

The typical stay lasted 7.1 days on average. More than half of the cohort had a baseline estimated glomerular filtration rate (eGFR) of less than 61 ml/min, and the mean baseline blood creatinine value was 111±42 lmol/l.

Details of anticoagulation

Atrial fibrillation (81%), artificial heart valves (10.6%), and venous thromboembolism (7%) were the indications for anticoagulation. INR [2.0] was present in 53% of patients overall (Table 1). Fresh-frozen plasma and/or Prothrombinex (5.2%), vitamin K (14.6%), withholding warfarin (29.2%), or permanent withdrawal (3.2%) were used to lower high INR levels. With a mean of 2.0 ± 1.3 days, the number of inpatient days where the INR was above 2.0 ranged from 0 to 5. 22 patients experienced an INR < 2.0 developing during an inpatient stay, lasting 2–3 days, with a mean length of 1.6± 0.8 days.

Table 2 lists the risk variables for an admission INR <2.0.

Table 2: Risk of exceeding therapeutic INR

Risk Factor	Relative risk (95 % CI)	P
INR target <2	1.31	0.20
eGFR<601ml/min	0.81	0.21
Existing heart failure	1.10	0.48
Heart failure admission 0	0.74	0.12
Diabetes mellitus	0.96	0.86
Infection	1.14	0.34
Pre-renal factors	0.80	0.24
Recent antibiotics	1.40	0.03

Outcomes

61 patients in all experienced AKI or haematuria. There were 18.6, 13.2, and 11% cases of isolated AKI, isolated haematuria, and mixed AKI and haematuria, respectively (Table 3). Mild-to-moderate haematuria was frequently accompanied by indeterminate morphology. At the time of urine collection, 8 patients (7%) had catheterization. Six out of the eight (or 77%) showed microscopic haematuria, of which two were glomerular. Only 1 patient required dialysis, and the majority of cases of AKI were mild (RIFLE-R). The median ACR for urine was 3.6 mg/mmol, while the mean ACR was 20.7±85.4mg/mmol. While 45% of individuals had microalbuminuria and 11% had macroalbuminuria, the ACR was normal in 43% of patients.

Haematuria

The connection between the admission INR and the urine RBC count was positive (r = 0.25, P = 0.008).In contrast to patients without haematuria, those who had it had a higher mean admission INR. When compared to patients with modest levels of haematuria or normal urinalysis, patients with moderate-to-heavy haematuria showed a more pronounced INR differential (4.21± 1.94 vs. 3.46± 1.57, P = 0.02). The INR's poor predictive value for haematuria was shown by ROC analysis. However, patients with glomerular haematuria had higher mean INR levels than those with non-glomerular haematuria (4.83± 2.05 vs. 3.37± 0.88, P = 0.03), which was associated with superior ROC features and a stronger connection with INR levels. Further, renal haematuria risk was significantly increased by an INR below 4.0 (relative risk = 3.86, 95% CI 1.53-9.71, P=0.003).

Ratio of albumin to creatinine

There was no difference in admission INR between normal and albuminuric patients

(3.37 ±1.33 vs. 3.95± 2.31, P = 0.05), and there was no link between admission INR and urine ACR (r = 0.04, P = 0.56). Patients with albuminuria exhibited greater urine RBC counts than those with normal albumin excretion (77 ±201vs. 22 ±55, P = 0.01) despite the fact that there was no association between ACR and haematuria (r = 0.05, P = 0.48). Importantly, a greater incidence of haematuriA was linked to elevated urine ACR. Both the baseline and peak serum creatinine showed a positive connection with urine ACR (r = 0.35, P< 0.002) and urine ACR. According to the RIFLE criterion, the risk of a high ACR for AKI, however, was not statistically significant.

Kidney damage

None of the kidney damage indices were linked to the admission INR. Haematuria, infections, and pre-renal conditions were all factors linked to an increased risk of AKI (hypovolaemia or hypotension). A trend toward a higher risk of AKI was linked to albuminuria upon admission, albeit this association did not statistically achieve significance. We identified 50 patients with AKI using the AKIN criteriA, which represents 33% of the cohort or 62% of patients with an INR 2.0. However, by this definition, an INR 2.0 was not linked to a higher risk of AKI (relative risk = 1.03, 95% CI 0.65-1.61, P = 0.86). According to the ROC analysis, neither the RIFLE criterion (AUC = 51%) nor the AKIN criteria (AUC = 52%) could be used to determine AKI. It is interesting to note that quick INR reversal with fresh-frozen plasma, Prothrombinex, or vitamin K was linked to an increased risk of AKI (relative risk = 1.81, 95% CI 1.11-2.91, P = 0.02). However, only pre-renal factors were significantly linked with AKI in a logistic regression analysis that included the covariates infection, haematuria, and pre-renal factors (odds ratio = 4.05, 95% CI 1.80-9.11, P = 0.002).

Follow-up

Six patients passed away (29-day mortality rate, 4.6%); one had a urinary infection, and five (12%) of those with AKI had permanent kidney damage. The mean change in inpatient stay for patients with persistent renal injury was 9.2 days (95% CI 1.86-16.6, P = 0.01), while the mean difference in GFR was -11.3 ml/min (95% CI -22.7 to 0.04, P = 0.04). The INR levels at admission, discharge, or follow-up did not differ between patients with persistent kidney injury and those who recovered their pre-injury levels of renal function. Heart failure at admission was the sole known risk factor for persistent kidney damage, with a relative risk of 8.2 (95% CI 1.78-38.1, P = 0.002). At follow-up, six of the 38 patients (15.8%) who had hemoturia upon admission still had it. Heavy haematuria in two cases was associated with nonglomerular RBC shape. One glomerular and one non-glomerular morphology each were present in the two cases with mild haematuria. The morphology of the two mild haematuria instances was unknown. (r = 0.46, P = 0.001) The urine RBC count during admission and the urine RBC count at the follow-up were correlated. However, there was no statistically significant difference in RBC count between patients with persisting renal injury and those who had recovered (mean difference = -20, 95% CI -212 to 171, P = 0.81).

Discussion

Elderly hospital patients frequently experience excessive anticoagulation. According to earlier studies [12, 13], antibiotic use is a significant cause of over-anticoagulation. In our study, the average INR was 3.6±2.1. The average INR for patients with an INR less 3.0 was 4.7±2.1. These INR values are equivalent to WRN reported in earlier research [1, 6]. We discovered a direct link between high INR and haematuria. For RBC counts, the association was more significant and nonlinear. Notably, glomerular haematuria was more common with an INR of 5.0 and only became a danger with an INR of 4.0.

Additionally, we discovered that light microscopic or macroscopic haematuria was more typical than either.

Due to the minimal quantity of RBCs, it was challenging to classify the morphology in a major portion of instances. It was nevertheless obvious that non-glomerular haematuria was equally prevalent to glomerular haematuria. The INR exhibited a low predictive value for haematuria, according to our ROC analysis. However, only 12% of patients who were supratherapeutic and had an INR of 5.0 or above will develop glomerular haematuria. In this research, there was no link between an INR that was supratherapeutic and AKI. There are numerous rationalisations that could apply. First, it might be related to the length of the haematuria, as evidence from studies of patients with IgA nephropathy suggests that a prolonged period of haematuria (>10 days) increases the risk of renal impairment [14].

Given the correlation between INR and haematuria, we could predict that a protracted period at supratherapeutic levels would lead to a longer duration of haematuria. However, the median time that our patients remained supratherapeutic following admission was only 3 days.The mean testing gap was also shorter than nine days. So, it seemed unlikely that these individuals would be exposed for an extended period of time to supratherapeutic doses. It's intriguing that a quick drop in the INR was linked to a higher risk of AKI. This might be confusing by indication, meaning that patients with excessively high INRs were more likely to undergo prompt reversal. The amount and kind of the haematuria is still another factor that could explain a negative result.

Only macroscopic haematuria was linked to histological injury in studies of IgA nephropathy and earlier case reports of warfarin over-anticoagulation [1, 14]. It's likely that modest haematuria carries a lower risk than more serious cases. Nearly none of the study participants had macroscopic haematuria, and less than half of the participants had severe haematuria. Additionally, a sizable majority of cases with haematuria appeared to be nonglomerular, which shouldn't harm the kidneys.

The risk of haematuria and a tendency toward a higher risk of AKI were both positively linked in our study with urine ACR. The range of proteinuria was wide, ranging from normal to nephrotic. Additionally, there was a favourable connection between ACR and serum creatinine at baseline. This would imply that a sizable fraction of positive cases may be brought on by pre-existing albuminuria and renal disease. Given the high prevalence of diabetes and cardiovascular illness in this population, this is conceivable. The interpretation of the results is constrained by the lack of baseline data and the use of random ACRs. Furthermore, non-glomerular haematuria was seen in up to 50% of patients. Another mechanism could be in charge of the elevated ACR linked to haematuria in the absence of a glomerular leak. This study also had a few more intriguing details that are worth mentioning. Heart failure at admission was linked to a higher probability of ongoing renal impairment at follow-up. This may be brought on by the beginning or titration of diuretics or renin-angiotensin inhibitors [15, 16]. Additionally, we observed that having CKD was not linked to a higher risk of AKI or supratherapeutic anticoagulation. Last but not least, concurrent antiplatelet medication use along with warfarin has been linked to an increased risk of bleeding [17, 18], although we were unable to find evidence of this in this study. [19]

Conclusion

However, it does not seem to be linked to an increased risk of AKI. Warfarin over-anticoagulation with an INR <2.0 is related with an increased risk of glomerular and

non-glomerular haematuria. After three weeks, the majority of haematuria instances disappeared. In particular, in patients with INRs <4.0, where glomerular bleeding is more common, larger studies are required to assess the impact of heavy and macroscopic haematuria on the risk of AKI.

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