Vitamin K antagonist-associated microscopic hematuria

Amir Shabaka,[1] Clara Cases-Corona,[1] Emily Larrea,[2] Karmele Arribalzaga,[3] Carmen Herrero Alonso,[4] Juan Manuel Acedo Sanz,[4] and Gema Fernandez-Juarez[1]

[1] Nephrology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [2] Faculty of Medicine, Rey Juan Carlos University, Madrid, Spain; [3] Hematology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [4] Clinical Analysis Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain

ABSTRACT

Background: Vitamin K antagonists (VKA) are the most widely used anticoagulants for the prevention of thrombotic events. Several renal adverse effects have been associated with the use of VKA. The main aim of our study was to explore the association between international normalized ratio (INR) levels and microscopic hematuria in patients with VKA.

Methods: We performed a cross-sectional study of patients treated with VKA that attended the outpatient clinic for routine INR control. A simple urinalysis was performed on the day of the INR control and the precise number of red cells in the urine sediment was quantified. Demographic data, kidney function tests, comorbidities, anticoagulant dose and concomitant treatment were registered.

Results: A total of 337 patients were included with median INR levels of 2.6 (IQR 2.1–3.3). 11.9% of the patients presented microscopic hematuria (≥14 RBCs/μl). There was a significant correlation between INR levels and the number of red blood cells in the urine sediment ($r = 0.201$, $p = 0.024$). In the univariate analysis, microscopic hematuria was associated with having an INR >3.5 (19% vs. 10.2%, $p = 0.046$), bacteriuria (15.2% vs. 3.6%, $p = 0.015$), leukocyturia (14.8% vs. 6.6%, $p = 0.026$), hypertension (16.2% vs. 9.5%, $p = 0.053$), and the use of renin-angiotensin system (RAS) blockers (6.9% vs. 17.2%, $p = 0.004$). Multivariate logistic regression showed an association between microscopic hematuria and RAS blockade (OR 0.38, CI 95% 0.163-0.886, $p = 0.025$), independent from INR levels, hypertension, leukocyturia or bacteriuria.

Conclusions: INR overdose was significantly associated with the presence of microscopic hematuria. RAS blockade is an independent protective factor for the presence of microscopic hematuria in anticoagulated patients.

Key Indexing Terms: Hematuria; Anticoagulation; Warfarin; Acenocoumarol; Renin-angiotensin system blockers. **[Am J Med Sci 2022;364(6):724–728.]**

INTRODUCTION

Vitamin K antagonists (VKA) are the most widely used anticoagulants in the daily clinical practice for the prevention of thrombotic events. Several renal adverse effects have been associated with the use of VKA, from hemodynamic effects due to massive urological hemorrhage associated with VKA overdose to non-hemodynamic effects that include glomerular hemorrhage and renal tubular obstruction due to red cell casts.

Gross hematuria is a frequent complication in anticoagulated patients. In a meta-analysis that included over 100,000 patients on treatment with oral anticoagulants, gross hematuria occurred in 26.7% of patients.[1] The predominant underlying cause was urological in 56% of patients with international normalized ratio (INR) <4 and 30% of patients with INR >4.

On the other hand, the association between anticoagulation and microscopic hematuria has been scarcely studied. In a study that included 296 patients, the prevalence of gross hematuria in patients treated with warfarin was similar to that in the control group and the published prevalence in the general population.[2]

Microscopic hematuria is a fundamental diagnostic and prognostic tool in the evaluation of glomerular diseases in our daily practice, and knowing the limitations in its interpretation in anticoagulated patients is essential for decision making for nephrologists.

The aim of our study was to establish an association between INR levels and microscopic hematuria in patients with VKA, and identify possible risk and protective factors associated with development of microscopic hematuria in these patients.

METHODS

We conducted an observational cross-sectional study in a cohort of patients undergoing treatment with chronic oral anticoagulation and regularly followed-up in the Hematology outpatient clinic at our centre. This study was approved by the ethical committee for clinical investigation at Hospital Universitario Fundación Alcorcón.

We included patients over 18 years old, anticoagulated with vitamin K antagonists (warfarin or acenocoumarol) who had a routine INR control at the Hematology outpatient clinic between October and December 2019. We excluded patients with direct oral anticoagulants or low molecular weight heparin, patients with permanent urinary catheters and patients with symptoms of urinary tract infection at the time of urine simple collection. All patients included in this study signed a written informed consent.

A spot urine sample was collected at the day of INR control. A urine dipstick test was performed with the usual 10 parameters: leukocytes, nitrites, urobilinogen, proteins, pH, red blood cells, specific density, ketone bodies, bilirubin and glucose. Urine sediments were studied with image recognition methods. Urine albumin-creatinine and calcium-creatinine ratios were also measured.

Urine samples were evaluated with Sedimax (Menarini), an automated urine microscopy analyser with a built-in digital camera that captures different high quality images by combining bright field and phase contrast microscopy, leading to more accurate results. Results are expressed in volume units as red blood cells per microliter (RBCs/μl). The cutoff point was established at 14 RBC/μl, which corresponds to 1−5 RBCs per field following a concordance study performed at our centre's laboratory.

We defined microscopic hematuria as the presence of ≥14 RBCs/μl in the urine sediment, leukocyturia as the presence of ≥14 white blood cells/μl in men and ≥18 white blood cells/μl in females. Hypercalciuria was defined as having a urine calcium-creatinine ratio >18 mg/mg.

Variables included in this study were collected from the patients' clinical records, including demographic data, past medical history, ongoing treatment and analytical variables such as the previous complete blood counts, coagulation profiles and urine analyses.

For statistical tests we used SPSS version 20.0 (Armonk, NY: IBM Corp). Continuous variables with normal distribution were expressed as mean and standard deviation, whereas variables which did not follow a normality distribution were expressed as median and interquartile range. We stratified the study sample into two cohorts according to the presence or absence of hematuria, and compared data between both cohorts. The statistical analysis for association was carried out by performing chi-square test for categorical variables, and Mann-Whitney U test for quantitative variables. The correlation between INR levels and hematuria quantification by flow cytometry was done by using the Spearman test. Statistical significance was defined when p was equal to or less than 0.05. Variables that were significant in the univariate analysis were included in a binary logistic regression analysis, with the dependent variable being the presence or absence of microscopic hematuria.

RESULTS

The study population included 337 patients who received oral anticoagulation with VKA. The mean age was 68.6±12.2 years, 35% of patients were over 75 years of age, and there was a slight predominance of female patients (51%). 95% of patients were treated with acenocoumarol and 5% with warfarin. 54 patients (16%) were additionally taking an antithrombotic agent; 38 patients were on aspirin, 13 were on thienopyridines and three patients were taking dual antiplatelet therapy. Most patients (65%) were hypertensive whereas only 28% had diabetes mellitus and 23% had a known urologic condition.

The most frequent indication for anticoagulation was mechanical heart valves (43.6%) followed by nonvalvular atrial fibrillation (26.7%) and deep venous thrombosis or pulmonary embolism (14.2%) (Table 1). Median INR levels were 2.6 (interquartile range 2.1−3.3). 49.6% of patients were within the target INR range, while 25.5% were below the target range and 24.6% were above it. 4.7% of patients had an INR deviation over 50% of the superior limit of the target INR range. The median vintage time of anticoagulation was 50 months (interquartile range 7−159). Seventy-nine patients (23%) had suffered from previous bleeding events.

Table 1. Distribution of indication for anticoagulation.

Indication	n (%)	Target INR range
Non-valvular atrial fibrillation	90 (26.7)	2-3
Atrial fibrillation/flutter with prosthetic valve	147 (43.6)	2.5-3.5
Pulmonary embolism/deep venous thrombosis	48 (14.2)	2-3
Antiphospholipid syndrome	23 (6.9)	2-3
Other causes (nephrotic syndrome, arterial embolism, coagulation abnormalities)	29 (8.6)	2-3

>2 indications = 28% of patients.

Table 2. Baseline characteristics of the global cohort and stratified according to presence or absence of microscopic hematuria.

Variable	Total (*n* = 337)	Hematuria (*n* = 40)	No hematuria (*n* = 297)	*p*
Age (years)	68.6 ± 12.2	71.6 ± 12.1	68.2 ± 12.2	0.718
Female sex *n (%)*	172 (51)	23 (57.5)	149 (50.2)	0.384
Hypertension *n (%)*	220 (65.3)	21 (52.5)	199 (67)	0.053
Diabetes mellitus *n(%)*	93 (27.6)	10 (25)	83 (28)	0.687
Known kidney disease *n (%)*	64 (19)	6 (15)	58 (19.5)	0.493
Known urological disease *n (%)*	77 (22.8)	11 (27.5)	66 (22.2)	0.455
Oral anticoagulation vintage *(months)*	49.8 (7–159)	91.7 (12.1–187.6)	46.6 (7–153.4)	0.310
Weekly dose *(mg/week)*	14 (10.5–19)	11.5 (8.2–17)	14 (10.5–20)	0.012
INR	2.80 ± 1.05	3.05±1.13	2.77±1.03	0.114
INR >3.5 *n(%)*	63 (18.7)	12 (30.0)	51 (17.2)	0.046
Serum creatinine *(mg/dl)*	0.95 ± 0.32	0.97 ± 0.42	0.95 ± 0.31	0.118
Urine albumin-creatinine ratio *(mg/g)*	9.5 (3.4–2.1)	14.6 (5.8–67)	9.3 (3.1–30.7)	0.054
Urine calcium-creatinine ratio *(mg/mg)*	0.06 (0.03–0.11)	0.05 (0.03–0.10)	0.06 (0.03–0.11)	0.762
Antiplatelet treatment *n (%)*	48 (14.2)	3 (7.5)	45 (15.2)	0.194
RAS blockade treatment *n (%)*	174 (51.6)	12 (30)	162 (54.5)	0.004

INR: International normalized ratio. RAS: Renin-angiotensin system

Microscopic hematuria was present in 40 patients (11.9%). Median RBC concentration in the urine of patients with microscopic hematuria was 33 RBCs/μl (interquartile range 22–59). In patients without microscopic hematuria the median concentration of RBCs in the urine sediment was 7 RBCs/μl (interquartile range 0–13). Table 2 shows the demographic, clinical and laboratory characteristics of the whole cohort and stratified according to the presence or absence of microscopic hematuria.

Microscopic hematuria was more frequent in patients with INR >3.5 than in those with INR < 3.5 (19% vs 10.2%, $p = 0.046$). There was a positive correlation between INR levels and the number of red blood cells in the urine sediment (r Spearman=0.119, $p = 0.029$). Fig. 1 shows the proportion of patients with microscopic hematuria according to age group and INR. Although microscopic hematuria was more frequent when INR was >3.5 for all age groups, this association was stronger in younger patients. Hence, in patients with INR <3.5 only 6.7% of patients below 65 years had microscopic hematuria, compared to 7.7% of patients between 65 and 75 years and 15.8% in those older than 75 years. On the other hand, in patients with INR >3.5 microscopic hematuria was present in 21.4%, 15.4% and 21.7% in the three age groups respectively.

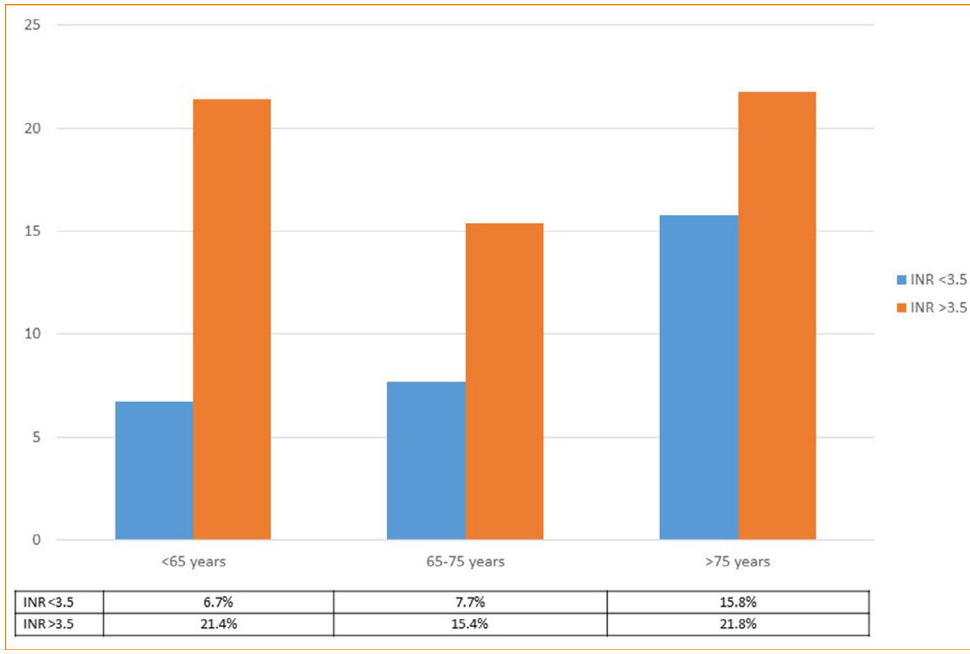

FIG. 1. Proportion of patients with microscopic hematuria according to age group and international normalized ratio (INR).

Despite that none of the patients included in the study presented with symptoms of urinary tract infection or lower urinary tract syndrome when the specimens were obtained, microscopic hematuria was significantly more frequent in patients with asymptomatic bacteriuria (15.2% vs. 6.3%, p = 0.015), or leukocyturia (40% vs. 18.2%, p = 0.001). Thirty-three patients included in the study had hypercalciuria (9.8%). However, microscopic hematuria was not more frequent neither in patients with hypercalciuria (10%) nor in patients with history of recurrent renal stones. Microscopic hematuria was not associated with cardiovascular risk factors such as hypertension, diabetes or hypercholesterolemia, or with cardiovascular comorbidities.

In the multivariate logistic regression analysis the presence of microscopic hematuria was associated with an INR >3.5 (OR 2.55, IC95% 1.12–5.81) after adjusting for other variables such as age, hypertension, albuminuria, anticoagulant dose, previous hemorrhagic events, the presence of leukocyturia and bacteriuria. Microscopic hematuria was also associated with a past history of gross hematuria (OR 4.28, IC95% 2.02–9.06). On the other hand, treatment with renin-angiotensin-aldosterone (RAS) blockers was associated with a lower risk of microscopic hematuria (OR 0.35, IC95% 0.14–0.84) (Table 3).

DISCUSSION

In this study, the prevalence of microscopic hematuria in anticoagulated patients with VKA was 11.9%, with an increasing prevalence of hematuria in patients with INR >3.5. On the other hand, we found that hematuria was less frequent in patients receiving RAS blockers.

The prevalence of hematuria in the general population varies according to the age group, from 0.5 to 2% in children to 0.2–21% in adults.[3] Differences in age distribution and morbidity between populations of previous studies justify this wide range. In our study, the prevalence of microscopic hematuria (11.9%) was similar to that reported in the general population, but we found that those patients who were over-anticoagulated with INR >3.5 presented more frequently with microscopic hematuria (19%) than those with INR <3.5 (10.2%). Anticoagulation has seldom been considered a risk factor for developing microscopic hematuria. However, there is a wide consensus on the predisposing role of anticoagulation for gross hematuria.[1] In a series of 215 patients that were admitted for gross hematuria, 24% were under anticoagulant therapy among which a non-urological cause for hematuria was found in 44% of patients when INR was below 4, whereas it rose up to 70% in those patients whose INR was above this level.[4]

Glomerular hematuria is usually associated with other signs such as proteinuria, red cell casts in the urine sediment or decline in glomerular filtration rate. However, it is well known that persistent microscopic hematuria could be the sole manifestation in some glomerular diseases such as IgA nephropathy or collagen glomerulopathies. In three series that included 240 patients with isolated microscopic hematuria, without proteinuria and with normal kidney function, after ruling out urological causes IgA nephropathy was found in 20–30% of cases and collagen glomerulopathies in 4-43%.[5–7]

Although our study did not include a control group to compare the prevalence of microscopic hematuria in non-anticoagulated patients, we found that its frequency increased in patients with higher INR levels. Considering the broad glomerular surface, it could be speculated that

Table 3. Risk factors for presence of microscopic hematuria.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age	0.974	0.944–1.005	0.101	0.966	0.931–1.003	0.073
Sex *(1= male)*	1.344	0.690–2.618	0.385			
Hypertension	1.837	0.944–3.576	0.073	1.492	0.616–3.614	0.376
Serum creatinine (mg/dl)	0.822	0.309–2.188	0.695			
Urine albumin-creatinine ratio *(mg/g)*	0.999	0.998–1.000	0.146	1.000	0.998–1.001	0.579
Urological disease	0.753	0.357–1.588	0.457			
Anticoagulant weekly dose *(mg/week)*	1.015	0.980–1.052	0.402	0.997	0.961–1.035	0.885
INR >3.5	2.067	0.986–4.335	0.055	2.546	1.115–5.812	0.027
Anticoagulation vintage *(>50 months)*	1.418	0.728–2.763	0.304			
Bacteriuria	2.637	1.174–5.921	0.019	1.741	0.668–4.538	0.257
Leukocyturia	3.000	1.493–6.029	0.002	1.930	0.837–4.452	0.123
Previous hemorrhagic event	4.034	2.039–7.980	<0.001	4.276	2.019–9.056	<0.001
Hypercalciuria	1.027	0.341–3.090	0.962			
Antiplatelet treatment	0.454	0.134–1.536	0.204			
RAS blockade treatment	0.357	0.175–0.729	0.005	0.347	0.143–0.839	0.019

INR: International normalized ratio. RAS: Renin-angiotensin system

several cases of anticoagulation-associated hematuria are of glomerular of origin, especially in presence of underlying diseases affecting the glomerular endothelium. Therefore, when hematuria appears in anticoagulated patients with a glomerular disease, it should be considered whether it is an incipient relapse or the patient is stable and hematuria is associated with the anticoagulation dose. Thus, a comprehensive evaluation of hematuria in patients with glomerular diseases should include INR levels on the day of the urine sediment analysis.

Recently, a new entity named anticoagulant-related nephropathy has been described, defined as an acute kidney injury caused by massive glomerular hemorrhage induced by anticoagulation.[8] The first reported cases were patients with gross hematuria, acute kidney injury, and extremely elevated INR levels. Kidney biopsies showed normal glomeruli with abundant intratubular red cell casts predominantly in distal tubules.[9]

Animal model studies have demonstrated that the tubular lesion occurs due to oxidative stress, even in absence of tubular obstruction, being particularly deleterious in previously injured tubules.[10] In a cohort of patients, the presence of atrial fibrillation was a main risk factor for progression to end-stage kidney diseases, especially in patients with previously known CKD.[11] This study did not delve into the mechanism for CKD progression, a possible explanation would be the implication of anticoagulant-related nephropathy, in the form of mild recurrent acute kidney injuries produced by temporary elevations in INR levels, or due to a chronic injury caused by persistent glomerular haemorrhage. The evaluation for hematuria in these patients could have aided in supporting this hypothesis and could have helped in preventing CKD progression.

The main limitation of this study was the absence of baseline data prior to the start of anticoagulation to clarify whether hematuria was present before anticoagulation or rather induced by VKA. Another limitation was the absence of longitudinal data to compare the variations in the degree of hematuria at each time point according to INR levels, which would be needed to further confirm the association between INR levels and hematuria.

In this study, patients treated with RAS blockers had a significantly lower prevalence of hematuria. This association has not been reported before, although several studies have shown their beneficial effects in glomerular diseases such as IgA nephropathy and type IV collagen nephropathy in which the presence of hematuria is a key element, improving their long-term prognosis.

CONCLUSIONS

In conclusion, isolated microscopic hematuria was frequent in anticoagulated patients with VKA. Excessive anticoagulation (INR >3.5) was significantly associated with the prevalence and intensity of microscopic hematuria. Therapy with RAS blockers was an independent protective factor for developing hematuria in anticoagulated patients. All patients with microscopic hematuria regardless of the INR should be studied etiologically, although in patients under follow-up for glomerular pathology associated with hematuria, knowledge of the INR can help to contextualize the variations in its intensity.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no conflicts of interest to disclose.

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Corresponding author. Amir Shabaka, Servicio de Nefrología, Hospital Universitario Fundación Alcorcón. C/Budapest, 1. 28922 Alcorcón, Madrid, Spain; (E-mail: amirshabaka@hotmail.com).