

Macroscopic hematuria in patients on anticoagulation therapy

Boris Seryozhev Mladenov¹, Valeri Mariyanovski¹, Valeria Hadzhiyska²

¹UMHATEM "Pirogov", Sofia, Bulgaria

²University Hospital Alexandrovska, Medical University, Sofia, Bulgaria

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Corresponding author

Boris Mladenov
UMHATEM "Pirogov"
Bul. Tottleben 21
1000 Sofia, Bulgaria
phone +35 988 455 1093
boris_mladenov@abv.bg

Introduction Visible hematuria is not rare in patients on anticoagulant therapy. There is no consensus regarding the diagnostic approach for them; some authors suggest restricted volume of diagnostic procedures because of the low number of urological etiology found. Some antibiotics have been reported to potentiate the effect of oral anticoagulants.

Material and methods The study addresses the need for urological assessment of patients on anticoagulation therapy and the possible role of some drugs administrated simultaneously with an oral anticoagulant, for the onset of macroscopic hematuria. Patients hospitalized with hematuria, both with or without anticoagulation therapy, were investigated and followed up.

Results The onset of hematuria depends on the monitoring of oral anticoagulation. INR (International Normalized Ratio) value corresponds with the probability of non-urological etiology, where INR>4 carries relatively low risk for urological and malignant etiology. Some antibiotics may influence the anticoagulation effect, so INR value may be elevated and hematuria may occur.

Conclusions Anticoagulation therapy should be administrated carefully and individually. The risk of urological etiology of hematuria is lower in patients on oral anticoagulants (especially when INR >4), however, it is not zero.

Key Words: hematuria ↔ anticoagulants ↔ International Normalized Ratio ↔ diagnostic volume

INTRODUCTION

Currently, an increasing number of patients are on anticoagulation or antiplatelet therapy because of cardiovascular disease [1]. Anticoagulation is the target of treatment in various diseases, which leads to overcoagulation and vascular incidents, sometimes with a fatal outcome. The most common anticoagulants used in ambulatory conditions are low molecular weight heparins administrated subcutaneously and oral anticoagulants – antagonists of vitamin K. Low molecular weight heparins show many advantages to unfractionated heparin, such as a longer half-life of anti-Xa-activity, higher bioavailability, as well as a lower risk of heparin-induced thrombocytopenia [2]. Oral anticoagulants, or vitamin K antagonists, inhibit the enzyme vitamin K-epoxide reductase, which prevents the transformation of vi-

tamin K to vitamin KH₂. The latter is needed for the activation of the vitamin K dependent coagulation factors [3] – II, IV, IX, X, protein C and S. When anticoagulants are administered, the prothrombin time (PT) is monitored, based on the standardized WHO indicator – INR (International Normalized Ratio). There are two anticoagulation levels recommended – lower (target INR between 2.0 and 3.0), and higher (INR between 2.5 and 3.5) [4] (Table 1).

The frequency of macroscopic hematuria in patients on anticoagulants cannot be determined uniquely: in available literature it varies between 2% and 24% [5, 6]. Logically, one of the most common complications of overdosing anticoagulant therapy is hematuria, especially when oral anticoagulants are used [7]. We aim to investigate the relation of the administration of anticoagulants and the manifestation of non-traumatic macroscopic hematuria, to determine

in which of the cases there is urological etiology, what is the risk of urological malignancy and in which patient groups it is more pronounced. Hemostatic treatment in patients with hematuria and anticoagulation therapy according to the INR was also evaluated. The impact of concomitant administration of antibiotics or antiplatelet drugs was assessed.

MATERIAL AND METHODS

215 patients hospitalized with non-traumatic hematuria were enrolled prospectively for 2 years (from October 2012 to October 2014). All patients were investigated until the urological etiology of the hematuria was identified or rejected, all of them having received at least one abdominal and kidney ultrasonography and, where necessary, KUB, CT and/or CT-urography, MRI, cystoscopy, retrograde pyeloureterography, and diagnostic ureteroscopy. All cases of patients on anticoagulation

therapy were analyzed. A detailed patient history for concomitant conditions requiring anticoagulant usage, their dosage and patient dosage compliance were evaluated, as well as the concomitant administration of other drugs at the time of the hematuria manifestation. The dynamics of the coagulation status of patients (INR) were followed up every two days until reference ranges were achieved. Data about the etiology of the hematuria in groups with or without anticoagulation therapy was juxtaposed in an attempt to assess the need of a full diagnostic volume approach in patients on anticoagulation therapy.

SPSS 17.0 was used for statistical processing. Methods used: descriptive analyzes, graphic analyzes, Student T-test, Mann–Whitney test.

RESULTS

Out of all 215 patients, 131 were male and 84 female, aged between 29 and 93 (mean 61 years). 52 out of all of the hospitalized patients (24%) were on anticoagulation therapy, 34 males and 18 females, aged 44 to 87 (mean 68 years).

Three groups of anticoagulants were taken by the patients: unfractionated heparin (2 patients), inhibitors of factor Xa, incl. low molecular weight heparins (12 patients), and antagonists of vitamin K/oral anticoagulants (38 patients) – most frequently acenocoumarol.

The indications for anticoagulant therapy are shown in Table 2. 63% of the patients have more than one indication for anticoagulant usage.

According to the patient history, 27% of the patients treated with antagonist of vitamin K strictly complied with the dosage and were regularly monitored by a physician (assessing their INR). The other 73% reported omissions for varying reasons. Logically INR is higher in patients with inadequate thera-

Table 1. Main indications for using anticoagulants and the target recommended INR (International Normalized Ratio)

INDICATIONS	INR
Prophylaxis of vein thrombosis	2.0–3.0
Treatment of vein thrombosis	2.0–3.0
Treatment of pulmonary embolism	2.0–3.0
Prophylaxis of systematic embolism	2.0–3.0
acute heart attack	
valvular heart disease	
atrial fibrillation	
dilated cardiomyopathy (DCM)	
Prosthetic heart valves	
mechanical valves	2.0–3.0
tissue (biological) valves	2.5–3.5
Antiphospholipid syndrome (APS) (recurrent deep vein or arterial thrombosis)	2.5–3.5

Table 2. Indication for administration of an anticoagulant in patients, hospitalized with hematuria

Leading indications/disease	Number (n)/ % of all	Males (n)	Females (n)
Deep vein thrombosis	17/ 33%	10	7
Status post pulmonary embolism	10/ 19%	7	3
Heart diseases:			
– Heart rhythm disorders			
– Valvular disease			
– Status post heart attack	20/ 38%	13	7
Heart valve prosthesis	5/ 10%	4	1
TOTAL:	52/ 100%	34/ 65%	18/ 35%
From them with more than one indication for anticoagulation therapy	33/ 63%		

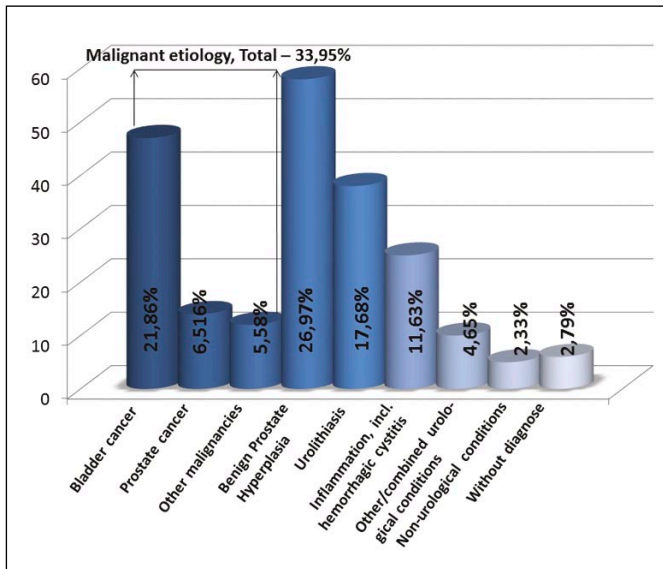


Figure 1. Distribution of patients with hematuria according to etiology (hospitalized patients without anticoagulation therapy).

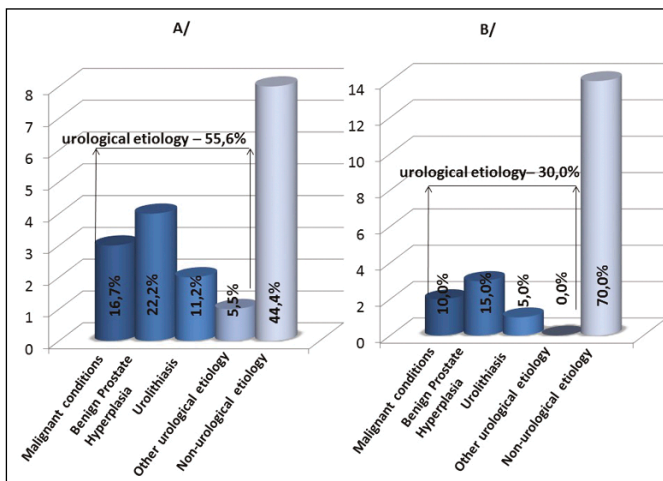


Figure 2. Distribution of patients with hematuria according to etiology (hospitalized patients with oral anticoagulation therapy) A. INR <4; B. INR >4 at the time of admission (INR – International Normalized Ratio).

py monitoring, mean INR 4.02 ± 1.24 , in contrast to 3.63 ± 2.67 in those with strict monitoring, $p = 0.005$. In non-traumatic hospitalized patients without anticoagulation therapy, urological etiology for the hematuria was found in 96% of the cases where malignancy was found in 73 cases (44.8%) with bladder carcinoma being the most frequent (Figure 1). All but one of the 12 patients using factor Xa inhibitor/fractionated heparins did not overdose their therapy, which was administrated subcutaneously or orally. Urological pathology was found in all

of them, except for the case with oral Xa inhibitor use, and the malignancy was 33%.

Out of the patients on an oral antagonist of vitamin K and INR <4 at the time of admission, 55% were diagnosed with urological disease causing hematuria with malignancy of 17%, bladder cancer again being the most frequent. For patients with INR >4 the results were 30% and 10%, respectively (Figure 2).

7 of the patients on oral anticoagulants had received antibiotics (5 beta-lactams and 2 – fluorquinolones) as a concomitant therapy before and at the time of the hematuria onset. The analysis of the INR as a criterion shows a statistically significant difference between the group on concomitant antibiotics and the group not using either of them ($p = 0.032$).

Oral anticoagulants were discontinued in all patients with hematuria and replaced with low molecular weight heparins (enoxiparin), 40 mg or 60 mg, in 22 patients – according to the protocol in the department, aiming to reduce the risk of thromboembolic incidences. The other 16 did not receive anticoagulation therapy until INR dropped within the reference ranges (below 3.0 or 3.5). The comparison between the number of hospitalization days in both groups (8.7 and 9.1 respectively) did not show any statistical significance ($p = 0.34$). In either group no thrombotic complications were registered.

DISCUSSION

Investigating patients with hematuria hospitalized in non-urological departments, Antoniewicz et al. [8] reported 65% of them to be on anticoagulation therapy. Their results suggest that the current role of visible hematuria as a manifestation of serious and potentially dangerous urological conditions requiring detailed investigation, should be reevaluated for patients on anticoagulation therapy. In those individuals, they found only 19% urological etiology, where the cost/effectiveness analysis questions the necessity of a full volume diagnostic algorithm. Other authors report significantly higher percentage of serious urological etiology for such patients, varying between 17% and 82% [9, 10, 11]. Van Savage et al. recommend a full urological diagnostic assessment, where according to their data the probability of an underlying malignant condition may be about 30% [12]. According to our results, the risk of urological or uro-oncological etiology in patients with visible hematuria on oral anticoagulants (vitamin K antagonists) is lower, being clearly more pronounced when INR is higher than 4. However, it still exists and therefore, an adequate urological assessment is required. According to our findings, patients who apply their fractionated heparin adequately and

do not overdose it, the potential risk of urological etiology of hematuria is equal to the rest of the population. Various drugs are reported to increase the anticoagulation effect of anticoagulants when used simultaneously, interfering with anticoagulant pharmacokinetics – among them antibiotics from the penicillin group, cephalosporins II and III generation, and fluorquinolones [13]. Some authors find interrelationship between the patient history of recent usage of those antibiotics and the onset of visible hematuria in patients on anticoagulation therapy – their INR may be increased [14]. We find that some antibiotics may have such an effect, so INR value may be elevated and hematuria may occur. The substitution of the oral anticoagulants with a subcutaneous fractionated heparin does not seem

to increase the number of overall number of days of hospitalization and days with bleeding, respectively. This also seems not to be beneficial for reducing thromboembolic incidences in patients with INR over the lower therapeutic range.

CONCLUSIONS

Hematuria in patients taking anticoagulation drugs is not uncommon and the risk for the etiology to be of urological nature is lower than in the general population. However, that risk does exist and adequate urological evaluation is required.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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