Original Research Article

Assessment of haematuria and acute kidney injury associated with warfarin anticoagulation

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Abstract

Background: Warfarin is widely used as anticoagulant therapy to prevent primary and secondary thromboembolic events. The present study was conducted to assess haematuria and acute kidney injury associated with warfarin anticoagulation. **Materials & Methods:** 60 CKD patients (stages 2–4) who received chronic warfarin therapy were divided into 2 groups. Group I patients experienced a SC increase of ≥0.3 mg/dl and group II patients did not experience a SC increase of ≥0.3 mg/dl. Clinical parameters were measured before, during, and after the episode of INR >3.0. **Results:** There were 17 males and 13 females in group I and 20 males and 10 female sin group II. Hematuria at the time of abnormal INR was negative in 15 and 16, trace in 6 and 7, moderate in 4 and 5 and large in 5 and 2 in group I and II respectively. Treatment with warfarin recently initiated in 8 in group I and 4 in group II. For warfarin therapy was AF seen in 18 and 12, APL in 4 and 6, DVT in 6 and 8 and VR in 2 and 4. Diabetic nephropathy was seen in 12 and 8, HTN in 11 and 7 and glomerulonephritis in 7 and 15 in group I and II respectively. **Conclusion:** Chronic warfarin therapy that results in overanticoagulation is a risk factor for accelerated progression of CKD.

Key words: Hematuria, Kidney disease, Warfarin therapy.

Introduction

The use of warfarin to treat glomerulonephritis and various renal diseases was practiced in many countries in the 1970s and early 1980s. However, the pendulum may have swung the other way in recent years, with concern that warfarin may be detrimental to the kidneys in the long term. There is interest in the development of acute kidney injury (AKI) associated with warfarin therapy and possible poor outcomes in susceptible groups[1].

Warfarin is widely used as anticoagulant therapy to prevent primary and secondary thromboembolic events. Several adverse effects of warfarin therapy on the kidney have been reported; these adverse effects are collectively called warfarin-related nephropathy, which is characterized by hematuria and acute kidney injury[2]. This condition is more common in patients with than without renal diseases, including immunoglobulin A (IgA) nephropathy, nephrosclerosis, focal segmental glomerulosclerosis, and lupus nephritis. In most cases of warfarin-related nephropathy, red blood cell casts in the renal tubules obstruct urine flow, resulting in acute kidney injury; however, the glomeruli are not usually involved[3].

There is a wide variation is bleeding figures, depending on the INR target, patient characteristics and definitions used[4]. Patients with chronic kidney disease (CKD) have an increased risk of over anticoagulation as they spent less time in the therapeutic range, required frequent dose adjustments and had higher bleeding risk.

Briefly, AKI is typically considered by mechanism as prerenal, intrinsic (intrarenal), and postrenal (obstructive); all of which may be involved in warfarin-treated patients[5]. The present study was conducted to assess haematuria and acute kidney injury associated with warfarin anticoagulation.

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Materials & Methods

The present study was conducted among 60 CKD patients (stages 2–4) who received chronic warfarin therapy for any indication. Patients had at least 1 episode of International Normalization Ratio (INR) >3.0, serial measures of serum creatinine (SC) for at least 1 year before and at least 1 year after the INR >3.0, a SC measure within 1 week of the increase in INR >3.0.

Data related to patients such as name, age, gender etc. was recorded. Group I patients experienced a SC increase of ≥0.3 mg/dl and group II patients did not experience a SC increase of ≥0.3 mg/dl. Clinical parameters were measured before, during, and after the episode of INR >3.0. The definition of 'before' is the nearest value before the date when the INR was >3.0, and at least within 3 months before the INR >3.0. The definition of 'during' (at the time of) the episode of INR >3.0 are measures made at, or within 1 week of the date of the INR >3.0. Results thus obtained were subjected to statistical analysis. P value less than 0.05 was considered significant.

Results

Table 1: Patients characteristics

Parameters	Variables	Group I	Group II	P value
Gender	Male	17	20	0.07
	Female	13	10	
Hematuria at the time of abnormal INR	Negative	15	16	0.04
	Trace	6	7	
	Moderate	4	5	
	Large	5	2	
Treatment with warfarin recently initiated		8	4	0.01

Table 1 Fig 1 shows that there were 17 males and 13 females in group I and 20 males and 10 female sin group II. Hematuria at the time of abnormal INR was negative in 15 and 16, trace in 6 and 7, moderate in 4 and 5 and large in 5 and 2 in group I and II respectively. Treatment with warfarin recently initiated in 8 in group I and 4 in group II. The difference was significant (P< 0.05).

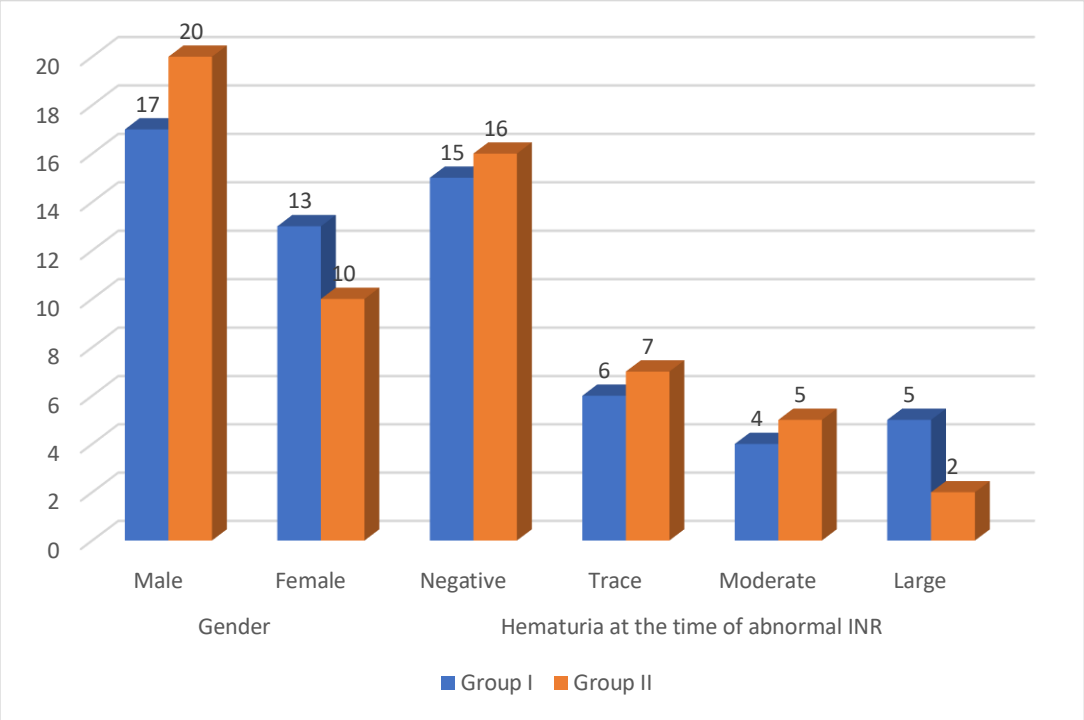

Fig. 1: Patients characteristics

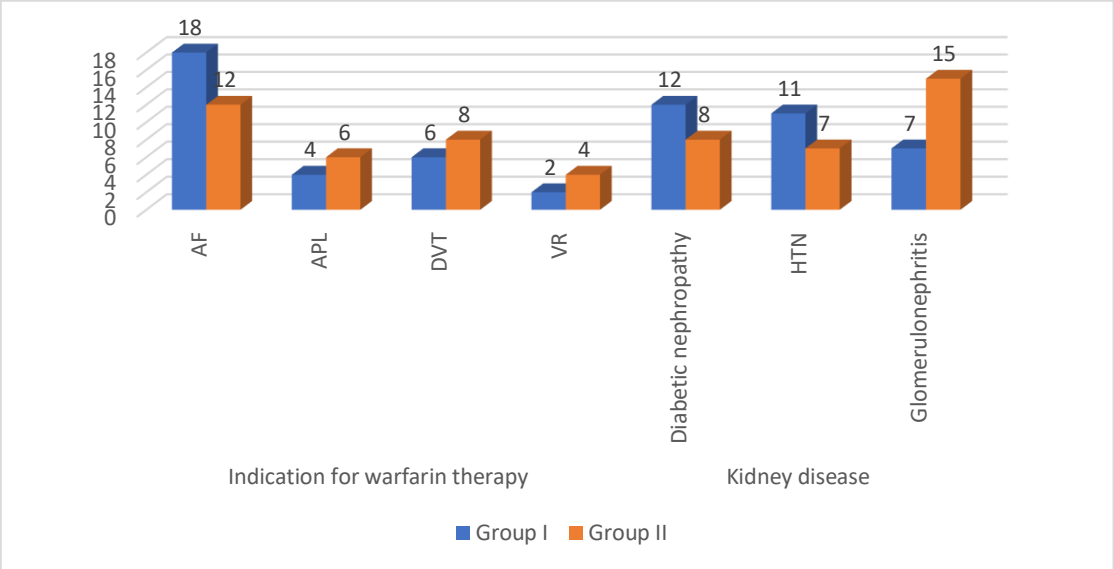

Fig. 2: Indication for warfarin therapy and kidney diseases

Table 2: Indication for warfarin therapy and kidney diseases

Parameters	Variables	Group I	Group II	P value
Indication for warfarin therapy	AF	18	12	0.02
	APL	4	6	
	DVT	6	8	
	VR	2	4	
Kidney disease	Diabetic nephropathy	12	8	0.05
	HTN	11	7	
	Glomerulonephritis	7	15	

Table 2, Fig 2 shows that for warfarin therapy was AF seen in 18 and 12, APL in 4 and 6, DVT in 6 and 8 and VR in 2 and 4. Diabetic nephropathy was seen in 12 and 8, HTN in 11 and 7 and glomerulonephritis in 7 and 15 in group I and II respectively. The difference was significant (P< 0.05).

Discussion

Despite initial scepticism, anticoagulant-related nephropathy is now considered in the lexicon of nephrologists[6]. If suggestions for diagnostic pathway are available, a standardised strategy of treatment is still lacking. Warfarin is an oral anticoagulant which inhibits vitamin K dependent γ-carboxylation of clotting factors II, VII, IX and X[7]. The main indications for warfarin are treating and preventing thromboembolism. Although effective, warfarin use is potentially complicated by supratherapeutic anticoagulation (over anticoagulation). Warfarin is strongly protein bound, mainly to albumin[8]. Albumin is a negative acute phase reactant and many illnesses reduce serum albumin. Warfarin is mainly metabolised by the CYP-2CP microsomal liver enzymes, which may be affected by a number of medications. Thus, medication interactions and medical conditions may predispose patients to supratherapeutic anticoagulation[9]. The prothrombin time, standardised as the International normalized ratio (INR) is used to monitor warfarin anticoagulation. Warfarin reversal may be achieved by administering vitamin K. Haemorrhage is the main complication of concern with warfarin therapy. The top three sites of bleeding are the oropharynx, soft tissue, gastrointestinal and urinary tract[10]. The present study was conducted to assess haematuria and acute kidney injury associated with warfarin anticoagulation.

We found that there were 17 males and 13 females in group I and 20 males and 10 female sin group II. Hematuria at the time of abnormal INR was negative in 15 and 16, trace in 6 and 7, moderate in 4 and 5 and large in 5 and 2 in group I and II respectively. Treatment with warfarin recently initiated in 8 in group I and 4 in group II. In one study, the average annual frequency of major bleeding was 3%, with 15% of major bleeding originating from the urinary tract. However, there is a wide variation is bleeding figures, depending on the INR target, patient characteristics and definitions used. Patients with chronic kidney disease (CKD) have an increased risk of overanticoagulation as they spent less time in the therapeutic range, required frequent dose adjustments and had higher bleeding risk[11].

We found that for warfarin therapy was AF seen in 18 and 12, APL in 4 and 6, DVT in 6 and 8 and VR in 2 and 4. Diabetic nephropathy was seen in 12 and 8, HTN in 11 and 7 and glomerulonephritis in 7 and 15 in group I and II respectively. Brodsky et al[12] analyzed serum creatinine (SC) and INR in 103 consecutive CKD patients on warfarin therapy in our Nephrology program from 2005 to the present. Forty-nine patients experienced at least 1 episode of INR >3.0. Of these, 18 patients (37%, Group 1) developed an unexplained increase in SC ≥0.3 mg/dl coincident with INR >3.0 (mean SC increase 0.61 ± 0.44 mg/dl); 31 patients (63%, Group 2) showed stable SC (mean SC change 0.04 ± 0.19 mg/dl). Subsequent CKD progression was accelerated in Group 1, but not in Group 2. The 2 groups were not different with respect to demographics, comorbidities, blood pressure, or therapies. However, African Americans were overrepresented in Group 1 (p = 0.035). Over anticoagulation is associated with faster progression of CKD in a high percentage of patients. Our results indicate the need for prospective trials. Nevertheless, we suggest that our findings are sufficiently compelling at this point to justify extra caution in warfarin-treated CKD patients to avoid over anticoagulation.

Conclusion

Authors found that chronic warfarin therapy that results in overanticoagulation is a risk factor for accelerated progression of CKD.

Conflict of Interest: Nil Source of support: Nil

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