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A centralised system for controlled administration and safety monitoring of coumarin therapy in haemodialysis units

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ABSTRACT

Aim: The prevalence of warfarin use among haemodialysis patients is reported to be increasing every year, with a higher complication rate than in the general population and a less than optimal patient and staff compliance.

Study Design: We designed a centralised system for drug prescription, on-site thrice weekly administration, surveillance and dosage management in dialysis patients, and performed a prospective evaluation, comparing it with the traditional daily dosage and control at the discretion of each attending nephrologist in another dialysis unit.

Patients and Methods: 21 consenting patients in Unit A and 11 in Unit B, with clinical indication for oral anticoagulation, were followed prospectively during 1 year.

Results: Atrial fibrillation was the more frequent indication for treatment. In Unit A 21 patients were treated to an average INR of 1.99, staying on range 37% of the follow-up time, compared to 32% of time in the 11 patients of Unit B. In Unit A there was 1 thrombotic event and no haemorrhages, and in Unit B 3 drop-outs due to lack of compliance, 1 myocardial infarction and 2 large haematomas.

Conclusions: A centralised system of prescription, monitoring and in-centre thrice-weekly administration of warfarin is feasible, guarantees compliance, is more effective and possibly safer than the traditional system of managing oral anticoagulation.

Key-Words:
Anticoagulation; atrial fibrillation; haemodialysis; warfarin.

INTRODUCTION

Warfarin is the mainstay of therapy for prevention of thromboembolic events in patients with all levels of kidney function. The prevalence of warfarin use among haemodialysis (HD) patients is reported to be 8 to 25%, with a large percentage presumably taking the drug for prevention of vascular access thrombosis, despite the lack of prospective data to support its use for this (or any other) indication[1,2].

Limdi *et al.*[3,4] recently reported that dialysis patients required significantly lower warfarin dosages (up to 20% reduction), exhibited poorer anticoagulation control, *i.e.* spent less time with

their INR within the target range, were at a higher risk for overanticoagulation (INR >4) and had a two-fold higher risk for haemorrhagic complications after adjustment for standard genotypic and clinical variables than patients with GFR >30ml/min/1.73m^2.

Atrial fibrillation (AF) is the most common arrhythmia in haemodialysis patients, with a prevalence in the 2009 USRDS report of 10%. According to USRDS, its prevalence is 10- to 20-fold higher than the general population, and has increased 6.6-fold in the last 15 years[5].

The risk of AF in dialysis patients is age and race-dependent (lower in blacks and Asians) and increases with several comorbidities, ranging in other series from 7 to 27%[6].

One-year mortality is twice as high among haemodialysis patients with AF as it is among those without (39% *vs*. 19%) and this increased risk, mainly related to thromboembolic events, has been constant during the last 15 years[5].

Data on coumarin use in haemodialysis patients with AF is scarce and inconclusive.

In 476 Italian HD patients, 27% with AF, a slight difference in the three-year stroke incidence was observed between AF (15%) and sinus rhythm (12%) patients[7]. On the other hand, in a Spanish HD population, those with AF revealed a significant increase from 5 (control) to 24 (AF) thromboembolic events per 100/pt/year (a 9.8-fold increase) and an increased 1.72-fold risk for mortality[8]. Quality adjusted life years (QALYs) increased by 0.15 years if haemodialysis patients with AF received warfarin, mainly due to stroke prevention[9].

Recognising the logistic difficulties in prescribing and monitoring warfarin treatment in a dialysis unit, as well as the dangers of erratic treatment compliance, we tried to design a centralised system of drug prescription, on-site administration, surveillance and dosage management in dialysis patients, and performed a prospective evaluation of its performance, comparing it with the conventional system of daily warfarin prescription and monitoring by every attending physician, as used in real life in another dialysis unit.

PATIENTS AND METHODS

This was a prospective trial, a real-life study, comparing a centralised system for controlled prescription, administration and monitoring of warfarin in Unit A with the traditional use of warfarin, a daily dose taken at dinner time, prescribed by each attending physician, who also carries the responsibility of monitoring for efficiency and safety, as performed in Unit B.

In both units, the decision to initiate warfarin therapy in each dialysis patient was up to his/her nephrologists´ clinical decision. Whenever a patient was prescribed coumarin (Varfine®) he was registered with the key person for this study in each unit.

Patients were assessed according to the CHADS2 score, which is recommended by the American Heart Association and European Society of Cardiology guidelines, to categorise the risk of thromboembolic events, and therefore the indication for anticoagulation. All patients had a score above 1, as recommended.

Per protocol, these were the indications and the INR targets' range proposed:

1. Atrial Fibrillation: INR Target 1.8-2.5
2. Mechanical heart valve prosthesis: INR Target 2.5-3.5
3. Severe congestive heart failure: INR Target 1.8-2.5
4. Deep vein thrombosis: INR Target 1.8-2.5

Unit A

Warfarin was administered on-site, directly supervised by our pharmacy nurse, three times per week at the end of each dialysis treatment, in the dose prescribed always by the same two physicians, the key-persons for that unit.

During the first month the prothrombine time (PT) was performed weekly (mid-week dialysis) in the beginning of dialysis, prior to needle heparinisation. After a month, PT was performed either bi-weekly or monthly, at the physician's discretion, and warfarin dose adjusted that same day by the research physician as deemed necessary.

For prothrombine time INR control, we used a bedside point of care Roche device, the CoaguCheck XS plus©.

Lab results were communicated to our key physician on the same day. He then recorded the results and adjusted warfarin dosage for the next period.

Unit B

Each attending physician prescribed warfarin to his patients. Patients took warfarin daily at dinner time as usual and PT monitoring and dose adjustment were performed according to *leges artis,* again at the discretion of each patient´s attending physician.

Prospective follow-up of the effectiveness and safety of anticoagulation

For each patient in each unit, the primary endpoint was to compare the percentage of time he/she had an INR in the predefined target range. Each INR result was considered representative of that patient's PT in the time period since the last determination.

Haemorrhagic episodes and their outcomes were recorded (only haemorrhages needing hospital admission or transfusion: CNS, GI tract, epistaxis, others)

We recorded each patient's identification, gender, age, indication for oral anticoagulation, CHADS2 score, chronological warfarin doses, INR results and clinical events (haemorrhagic episodes, acute coronary syndrome, stroke / TIA, hospital admissions, death, others).

Table I

CHADS score version 2, indications for oral anticoagulation in AF

CHADS2 Score	Points
Congestive Heart Failure	1
Hypertension	1
Age › 75 years	1
Diabetes	1
Stroke / TIA	2

RESULTS

Unit A had 301 patients at the end of the follow-up period on regular haemodialysis treatment and contributed 21 patients (6.9%) to the warfarin therapy protocol between March 1, 2010 and February 28, 2011.

Of the 14 male and 7 female patients, in 16 the indication for warfarin therapy was AF and the other 5 had clinical and laboratory (positive anti-phospholipid antibodies) thrombophilia. In those with AF, CHADS2 score was 2 in 6 patients, 3 in other 6 patients, 4 in 3 patients and 5 in 1 patient.

Average INR all along the year was 1.99±0.3.

As major complications we registered 1 deep venous thrombosis, 1 episode of calciphylaxis/calcific uraemic arteriolopathy (CUA) and no major bleeding. Two patients died during follow-up (9.5%), due to severe undernutrition and possible pulmonary embolism.

As side information, all patients maintained the same A-V vascular access (4 of them PTFE grafts) all along this year, without needing any endovascular or surgical intervention.

Unit B treats overall 222 patients and contributed 11 patients on oral anticoagulation (5%) to this study. As clinical indications for warfarin therapy, 5 patients have chronic AF, 5 have cardiac mechanical valve prosthesis and 1 case of thrombo-philia.

During 1 year of follow-up, Unit B registered 3 deaths due to unrelated reasons (sepsis, uterus malignancy and severe malnutrition) and 3 patients abandoned warfarin treatment due to lack of compliance. Major complications were a myocardial infarction and 2 large hematomas. As for follow-up, in unit A patients were treated with warfarin on average 30.5±19 weeks, in Unit B 25.9±21 weeks.

The average percentage of time patients were on target or off-range, during their treatment (their follow-up) in both units is recorded in table II.

Table II

Percentage of time on each INR target range

INR Target	% INR on range – Unit A	% INR on range – Unit B	*p* value
1.8-2.5	37.2±12.6	31.9±11.1	0.09
‹ 1.5	45.4±13.1	52.1±17.6	0.21
› 2.5*	18.6±7.2	16.1±7.1	0.15

*In the case of mechanical valves % › 3.5

DISCUSSION

In the DOPPS study cohort, 26.7% of all patients were on warfarin, aspirin or clopidogrel, despite little evidence to support their usage[11], despite the fact that bleeding may occur more frequently and with greater severity in these patients than the general population, leading to significant morbidity and mortality[12].

Current warfarin product labelling states that "no dose adjustment is necessary for patients with renal failure," although there is a high level of variability in dosing and responsiveness to the drug.

This is due to intrinsic patient factors such as genetics, age, weight, liver function, or extrinsic factors such as drug interactions, diet, or adherence to the medication as prescribed. Nonadherence rates are high in HD patients with pill burden, complex and dynamic medication regimens and poor patient motivation as the most pertinent factors[13]. Previous studies confirmed these high rates of medication nonadherence in dialysis patients with prevalences ranging from 19 to 99%, depending on the number of pills, cognitive impairment, depressive, or self-destructive mood.

Warfarin has a biologic half-life of 36 to 42 hours, allowing for potential prolongation of dosing intervals[14].

A recent study demonstrated that achievement of target levels of anticoagulation with thrice weekly warfarin administration compared with daily warfarin therapy (56.9 *vs*. 49.3% in target, respectively) appears safe and feasible[15]. They also showed that during the 48hr treatment intervals, patients were not exposed to wide fluctuations in anticoagulation levels. A thrice-weekly, in-centre, supervised monitoring and administration dosing regimen showed similar INR variability, higher percentage of time within targets and less time with INR › 4 *vs*. daily dosage.

Furthermore, HD patients are routinely exposed to heparin anticoagulation and the uraemic milieu has itself effects on the anticoagulation pathway. The interplay between this multiple factors may be what allows a thrice-weekly warfarin dosing strategy to effectively lead to anticoagulation.

In the traditional decentralised model of warfarin daily prescription and monitoring, our concern was not only patient adherence to a programme of daily intake at home of a drug that has constant dose changes, but also staff compliance with treatment protocol. As each attending nephrologist comes to the unit on average once or twice a week, it is in our experience very easy to miss lab monitoring ordering and results, as well as the appropriate dose adjustment schedule, creating the opportunity for major safety or efficiency breaches.

In our series we demonstrated that a centralised system with in-centre administration of medication is feasible, guarantees compliance, both from patients and staff, improves INR target range achievement, in itself the ultimate operational goal of the whole system and the end point of our study, without more adverse effects or less effectiveness. Compliance was a major issue in Unit B, with 27% patient drop-out due to difficulties with therapy adherence.

Unlike what is practiced in nondialysis patients, our INR was always a trough level, determined a few hours before next dose and our rather conservative target ranges had that in mind.

In Unit A patients were in target range 37% of the time, with only 3 determinations of INR above 4.0, definitely noninferior to Unit B performance, recording 32% of the time in target range with 6 determinations above 4.0.

In a large meta-analysis, involving more than 50,000 nonrenal disease patients, the INR was in the therapeutic range on average 64% of the time[16], dropping to 49.3% of the time in a large cohort of dialysis patients[15], both achieving a better result than our series, suggesting that we probably should

reduce the INR assessment intervals to no longer than two weeks apart.

The most serious adverse event we witnessed in Unit A was a case of severe calcific uraemic arteriolopathy, probably related to warfarin therapy in a patient with AF, which was immediately discontinued.

A lack of vitamin K results in undercarboxilated matrix Gla protein (MGP), which in turn promotes vascular calcification. Coumarin use has been consistently identified as a risk factor for calciphylaxis in HD patients[17].

Although we cannot compare the incidence of adverse events in both series due to small numbers and short follow-up, there were no haemorrhagic events in group A, and only two haematomas in group B. Although it is well proven that keeping INR inside ranges decreased the likelihood of anticoagulation-associated adverse events, more than 50% of all haemorrhagic or thromboembolic events occurred when the INR was inside our reference goal[18].

It is interesting that we registered such a low vascular access morbidity or failure in all these medicated patients. In several units abroad[1-4], warfarin is used with that so far unproven goal. Our results raise the possibility of looking prospectively to vascular access maintenance with oral anticoagulation

New, promising, but far more expensive antithrombine agents, such as dabigatran, are formally contra-indicated in dialysis patients, and therefore, it is most unlikely that these patients will benefit from much easier-to-control medication in the foreseeable future.

Conflict of interest statement. All the authors work in Fresenius Medical Care dialysis units. This study and its protocol was fully designed and executed by the authors, without any sponsorship or industry influence.

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