Journal of Applied Medical Sciences, vol.5, no. 3, 2016, 9-16
ISSN: 2241-2328 (print version), 2241-2336 (online)
Scienpress Ltd, 2016

Risks and Benefits of Warfarin Use for Cardiac Indications in Dialysis

Ahmad Chaaban[1], Nicole Gebran[1], Kareem Abdelmegid[1], Karem Soliman[1], Lina Agha[1], Saira Butt[1], Mohammed Budruddin[1], Hanan El Jack[1], Bassam Bernieh[1], Yousef Boobes[1], Samra Abouchacra[1], Mohammed Hakim[1], Hashem Tarifi[1], Qutaiba Hussain[1], Ahmed Ahmed[1] and Imran Khan[1]

Abstract

Background and Objectives: Anticoagulation in cardiac patients on hemodialysis (HD) presents a dilemma, with no clear guidelines to support an informed decision regarding warfarin use. Cohort studies revealed an association of a higher risk of bleeding and lack of improvement in stroke prevention in HD patients with atrial fibrillation treated with warfarin. The objectives of this study were to assess the efficacy and safety outcomes of warfarin use in cardiac hemodialysis patients.
Patients and Methods: We conducted a retrospective, comparative, observational, 2-arm controlled trial to assess the benefits and risks of warfarin use in two major dialysis units (>600 patients) in the UAE over 2 years. Primary outcome measures were incidence of bleeding and stroke. Secondary outcome measure was the percentage of patients achieving a target INR as set for the normal population. Arm 1 included all our adult patients on HD who were receiving warfarin for more than 6 months for cardiac indications (N=28; mean age 66.5 (11)). Patients on warfarin for other indications were excluded. Arm 2 consisted of a matching control group of patients with normal kidney (N=27; mean age 61.4(0.4)).
Results: Patients in Arm 1 presented with a higher incidence of bleeding than Arm 2 (6 vs. 3; P<.005). There was a higher incidence of stroke in Arm 2. More

[1] Tawam Hospital, Al Ain, United Arab Emirates

Article Info: *Received*: April 21, 2016. *Revised*: May 15, 2016.
Published online : July 15, 2016.

patients in Arm 1 received antiplatelet therapy with warfarin resulting in the increased bleeding risk. 25% of patients in Arm 1 achieved a median INR within target, while 96% achieved INR target in Arm 2 (median INR=1.9(0.5) vs. 2.4(0.3); P<.001). **Conclusions**: Anticoagulation in dialysis patients may not always be justified, the risks and benefits of treatment should be assessed carefully. Our study indicates an increased incidence of bleeding in HD patients. Most HD patients failed to achieve therapeutic INR, though their doses were similar to that of control; this may be attributed to variance in pharmacokinetic parameters. Our study is limited by small sample size; larger prospective studies will provide more robust evidence.

Keywords: warfarin, hemodialysis, anticoagulation, end stage renal disease, atrial fibrillation

1 Introduction

Atrial fibrillation is the most common cardiac arrhythmia in patients with end stage renal disease (ESRD). With a prevalence of 13 to 27%, it is an independent risk factor for a new stroke.[1] Patients with atrial fibrillation and severe chronic kidney disease have a higher risk for stroke and bleeding. Moreover, atrial fibrillation patients with severe chronic kidney disease and on dialysis, have a five-fold higher risk for a new stroke. [2] Warfarin is a vitamin K antagonist indicated for reducing the risk of stroke in patients with AF.[3]It is commonly used in dialysis patients as novel oral anticoagulants lack sufficient evidence for use in this high-risk population. Warfarin use has been shown to accelerate vascular calcification in CKD patients, which eventually may further increase the risk for ischemic stroke.[4, 5] Current observational studies on warfarin use in patients with AF undergoing dialysis and the risk for stroke and bleeding have conflicting results.[6, 7]AF management guidelines have yet to make strong recommendations regarding anticoagulation management for patients with AF undergoing dialysis.[8] Recognized limitations of warfarin, like frequent blood monitoring for INR, numerous food and drug interactions, uncertainty regarding benefit for reducing stroke risk and possible augmentation of bleeding risk, often raise concern about warfarin's safety and effectiveness in patients with AF undergoing dialysis. [9] Recent cohort studies revealed an association of a higher risk of bleeding and lack of improvement in stroke prevention in HD patients with AF treated with warfarin. It was observed that most of our dialysis patients on warfarin sustained a sub-therapeutic INR for long periods of treatment; a correlation between this low INR and incidence of cardiovascular disease was required, as well as a safety assessment regarding bleeding episodes.

2 Methods

We conducted a retrospective, observational, 2-arm controlled trial assessing the benefits and risks of warfarin use in 2 dialysis units (>700 patients) in the UAE over 2 years. Arm 1 (N=28; mean age 66.5 (11)) included all adult patients on HD and receiving warfarin for more than 6 months for cardiac indications. Patients in both arms had similar CHADS2 scores of ≥ 2. Twenty five patients in Arm 1 were receiving warfarin for AF and 3 for valvular heart disease. Patients on warfarin for indication other than cardiac were excluded. Arm 2 (N=27; mean age 61.4(20.4)) consisted of a matching control group of patients with normal kidney function and receiving warfarin for similar indications (Table 1). Primary outcome measures were incidence of stroke, MI, DVT, PE, bleeding, other cardiovascular events and death. Secondary outcome measure was the percentage of patients achieving a target INR as set for the normal population. Data was extracted retrospectively from Cerner. Analysis was done using Student T-tests and Chi-square tests. This study was approved by the Al Ain District Research Ethics Committee. The authors have no conflicts of interest to disclose.

3 Main Results

A comparable incidence of stroke and thrombosis was observed in both arms. Patients in Arm 1 presented with a higher incidence of bleeding than Arm 2 (6 vs. 3 cases (P<.005), 5 of which presented with major bleeding treated with vitamin K). There were more patients in Arm 1 receiving antiplatelet therapy with warfarin which may have resulted in the increased bleeding risk. Only 7(25%) of patients in Arm 1 achieved median INR within target (2-3 or 2.5-3.5), while 26(96%) achieved INR target in Arm 2, median INR was 1.9(0.5) in Arm 1 vs. 2.4(0.3) in Arm2 (P<.001). A higher incidence of stroke was observed in Arm 2 (Table 2). A high incidence of arteriovenous fistula stenosis was also noted in Arm 1 (11 (40%) patients).

4 Discussion

Atrial fibrillation is the most common sustained arrhythmia in clinical practice and carries a five-fold increased risk of stroke and three-fold increased risk of heart failure which leads to increased mortality. The outcome, effectiveness and safety of new oral anticoagulants in hemodialysis patients with AF is not well established.[10]

Compared with non-dialysis patients, dialysis patients with cardiac events (mainly atrial fibrillation), warfarin use did not reduce the risk of stroke, but was

associated with a higher risk for bleeding (21.4%) compared with non-dialysis patients (11.1%). Dialysis patients have an increased risk of bleeding and stroke due to several factors including platelet dysfunction, hypertension and diabetes. They also receive heparin routinely during dialysis. Long-term warfarin use on the other hand, can increase vascular calcification and accordingly the risk of stroke.[11, 12]

Shah et al retrospectively compared data from Ontario of 1626 dialysis and 204, 210 non-dialysis patients. Among dialysis patients, warfarin use compared to non-warfarin use was associated with a 55% higher risk of bleeding (adjusted HR 1.44, 95% CI 1.13 - 1.85) and was not associated with a lower risk for stroke (adjusted HR 1.14, 95% CI 0.78 - 1.07). Shah et al observed a 1.9 fold higher risk for the composite of stroke and death outcome with warfarin use.[12]

Genovesi et al reported in 134 HD patients out of 290 that warfarin use was not associated with increased mortality. During the follow-up of 115 patients, 8 patients died (4 strokes, 3 hemorrhagic and 1 thromboembolic). Antiplatelet therapy, but not warfarin was associated with increased mortality (HR 1.71, CI 1.1-2.64, P=.02). Estimated survival of those taking warfarin versus those who stopped tended to be higher (68.6% versus 49.3%, P=.07). Warfarin use was associated with a higher risk of bleeding (HR 3.96, CI 1.15-13.68, P=.03).[13]

Winkelmayer WC et al observed 237 patients with ESRD on HD and 948 propensity-matched non-users over 2287 person-years of follow-up. The occurrence of ischemic stroke was similar CHR 0.92, 95%; CI 0.61 to 1.37; where warfarin users experienced twice the risk of hemorrhagic stroke CHR 2.38, 95%; CI 1.15 to 4.96.[14]

In another study the Dialysis Outcomes and Practice Patterns Study (DOPPS) were used to assess the outcomes of hemodialysis patients with AF by warfarin exposure. Warfarin use was associated with increased stroke risk among patients over 75 years of age. CHR 2.17, 95%, CI 1.04 to 4.53 but not in patients younger than 75 years of age.[15]

Recently, Mac-Way et al observed 18 HD patients on warfarin were matched to 54 HD patients without warfarin. Aortic stiffness was measured by carotid-femoral pulse wave velocity at baseline and after a mean follow-up of 1.2 years. Warfarin therapy was independently associated with progressive aortic stiffness.[16]

To date, data is limited on the use of novel anticoagulants such as dabigatran, rivaroxaban and apixaban in dialysis patients. Chan et al compared patients with ESRD on hemodialysis on warfarin (n=8, 604), aspirin (n= 6, 018), dabigatran (n= 281) and rivaroxaban (n= 244). Bleeding rate was 83 events per 100 patient- years with dabigatran and 68.4 events per patient-years with rivaroxaban, while patients prescribed warfarin had a rate of 35.9 events per patient-years. Mortality rates from bleeding were 19.2, 16.2, 10.2, and 7.7 deaths per 100 patient years with dabigatran, rivaroxaban, warfarin and aspirin respectively.[17]

Recently, the Canadian Cardiovascular Society (CCS) AF guidelines (2012) made

conditional recommendation (based on low quality of evidence) that patients with AF undergoing dialysis should not routinely receive anticoagulant treatment for primary prevention of stroke.[18] Similarly, Improving Global Outcomes (KDIGO) guidelines advised against warfarin therapy for stroke prevention in dialysis patients due to lack of evidence and called for clinical trials in this area.[19]

4 Labels of figures and tables

Table 1: Demographics

Variables	HD Group (Arm 1) N= 28	Non-HD Group (Arm 2) N= 27	P value
Median weekly dose	23 mg	32 mg	.06
Mean weekly dose	27 (16) mg	37 (18) mg	.06
Gender	M= 15 F= 13	M= 16 F= 11	
Median age	64 years	67 years	.25
Duration of HD	26 (9) months		
Aspirin	19 (67.8%)	9 (33.3%)	
Clopidogrel	12 (42.8%)	6 (22.2%)	
Comorbidities			
Diabetes	17	9	.02
Cancer	2	1	.58
Stroke	0	2	.16
Vascular disease	20	17	.64

HD= Hemodialysis, M= male, F= female

Table 2: Summary of Results

End points	HD Group (Arm 1)	Non-HD Group (Arm 2)	P value
Median weekly INR	1.9	2.4	<.001
Mean weekly INR	1.9 (0.5)	2.4 (0.3)	<.001
Stroke	0	2	.98
MI	1	0	.31
DVT	0	1	.33
PE	2	0	.15
Other cardiovascular events	19	10	.01
Bleeding	6	3	<.005
Death	0	0	

HD=Hemodialysis, DVT= deep vein thrombosis, PE= pulmonary embolism, MI= myocardial infarction

5 Conclusion

The risks and benefits of anticoagulation with warfarin in dialysis should be assessed carefully. Our evaluation indicates an increased incidence of bleeding in HD patients vs. non-HD patients. This may be attributed to underlying pathology or concomitant antiplatelet therapy. Most HD patients failed to achieve therapeutic INR, though warfarin doses were similar in both groups, pharmacokinetic variation may play a role and hence benefits of treatment are uncertain. Our small sample size is a limitation; larger better designed trials may provide robust evidence to support an informed decision regarding anticoagulation in the dialysis population. Meanwhile, it is recommended to closely monitor dialysis patients on warfarin for bleeding indicators, especially if receiving concomitant antiplatelet therapy, where a lower than usual INR target may be considered. Otherwise, it is advised to maintain patients within therapeutic INR target as a sub-therapeutic level may increase the risk of cardiovascular events as observed in our patient

population. Establishing the safety and efficacy of novel anticoagulants in dialysis is a potential area for investigation and research.

References

[1] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991; **22**: 983-988.

[2] Seliger SL, Gillen DL, Tirschwell D, Wasse H, Kestenbaum BR, Stehman-Breen CO. Risk factors for incident stroke among patients with end-stage renal disease. *J Am Soc Nephrol.* 2003; **14**: 2623-2631.

[3] Mega JL. A new era for anticoagulation in atrial fibrillation. *N Engl J Med*. 2011; **365**: 1052-1054.

[4] Clase CM, Holden RM, Sood MM, Rigatto C, Moist LM, Thomson BK, et al. Should patients with advanced chronic kidney disease and atrial fibrillation receive chronic anticoagulation? *Nephrol Dial Transplant.* 2012; **27**: 3719-3724.

[5] Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. *J Am Soc Nephrol.* 2009; **20**: 872-881.

[6] Ng KP, Edwards NC, Lip GY, Townend JN, Ferro CJ. Atrial Fibrillation in CKD: Balancing the Risks and Benefits of Anticoagulation. *Am J Kidney Dis.* 2013; **62**: 615- 632.

[7] Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med.* 2012; **367**: 625-635.

[8] Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011; **80**: 572-586.

[9] Sood MM, Komenda P, Sood AR, Rigatto C, Bueti J. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? *Chest*. 2009 Oct;**136**(4):1128-33

[10] Liao Jo-Nan, Chao TF, Liu CJ, Wang KL, Chen SJ, Linet YJ et al. Incidence and risk factors for new onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. *Kidney Int*. 2014; **87**. 1209-1215

[11] Wetmore JB, Ellerbeck EF, Mahnken JD, Phadnis M, Rigler SK, Mukhopadhyay P, et al. Atrial fibrillation and risk of stroke in dialysis patients. *Ann Epidemiol*. 2013; **23**: 112-118

[12] Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation*. 2014 Mar

18;**129**(11):1196-203.

[13] Genovesi S, Rossi E, Pogliani D, Gallieni M, Stella A, Badiali F et al. The Nephrologist's anticoagulation treatment patterns/regimens in chronic hemodialysis patients with atrial fibrillation. *J Nephrol*. 2014 Apr; **27**(2): 187-92.

[14] Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and Safety of Warfarin Initiation in Older Hemodialysis Patients with Incident Atrial Fibrillation. *Clin J Am Soc Nephrol*. 2011 Nov; **6** (11): 2662-2668.

[15] Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int.* 2010 Jun; **77**(12):1098-106.

[16] Mac-Way F, Poulin A, Utescu MS, De Serres SA, Marquis K, Douville P et al. The impact of warfarin on the rate of progression of aortic stiffness in hemodialysis patients: a longitudinal study. *Nephrol Dial Transplant*. 2014 Nov; **29**(11):2113-20.

[17] Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation*. 2015 Mar 17;**131**(11):972-9.

[18] Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012; **28**: 125-136

[19] Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011; **80**: 572–586