WARFARIN DOSES IN THE INITIATION PHASE AMONG PATIENTS WITH HEART VALVE REPLACEMENT AND ATRIAL FIBRILLATION IN HOSPITAL PULAU PINANG

By

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AVR	Aortic valve replacement
BMI	Body mass index
CABG	Coronary artery bypass graft
CI	Confidence interval
CYP	Cytochrome P450
ES	Effect size
ICH	Intracerebral hemorrhage
ID	Identity
INR	International Normalized Ratio
ISI	International Sensitivity Index
MVR	Mitral valve replacement
OAT	Oral anticoagulation therapy
PT	Prothrombin Time
RM	Repeated measures
SD	Standard deviation
VKORC1	Vitamin K epoxide reductase complex subunit 1
WDI	Warfarin dose index
WHO	World Health Organization

DOS WARFARIN PADA FASA PERMULAAN DALAM KALANGAN PESAKIT PEMINDAHAN INJAP JANTUNG DAN FIBRILASI ATRIUM DI HOSPITAL PULAU PINANG

ABSTRAK

Penggunaan warfarin adalah sangat penting bagi pesakit yang menghidap fibrilasi atrium, pemindahan injap aorta dan pemindahan injap mitral. Walau bagaimanapun, penggunaan warfarin mungkin menyebabkan kesan sampingan yang bahaya seperti pendarahan dan ianya bergantung kepada dos warfarin. Memandangkan pendarahan lebih kerap berlaku di kalangan pesakit yang baru memulakan terapi warfarin dan perubahan dos juga dilaporkan berubah pada fasa permulaan terapi warfarin selepas pembedahan injap jantung, maka kajian ini mengkaji perubahan dos warfarin bagi pesakit yang memulakan terapi warfarin selepas pemindahan injap jantung dan fibrilasi atrium. Semua pesakit yang menghidap fibrilasi atrium, pemindahan injap aorta atau pemindahan injap mitral yang memulakan terapi warfarin pada tahun 2008 – 2010 di Hospital Pulau Pinang telah dipilih sebagai sampel. Sejumlah 137 pesakit telah dipilih sebagai sampel untuk kajian ini. Data yang dikutip termasuk umur, kaum, jantina, tarikh permulaan warfarin, indikasi warfarin, dos warfarin dan *international normalized ratio* (INR) untuk minggu pertama sehingga kedua-belas selepas permulaan warfarin terapi. Pesakit pemindahan injap jantung (aorta atau mitral) menunjukkan peningkatan dos warfarin bagi fasa permulaan warfarin terapi tetapi pesakit fibrilasi atrium tidak. Dos warfarin adalah berbeza antara 12 minggu pertama untuk kumpulan pemindahan injap aorta dan pemindahan injap mitral ($p < 0.001$) tetapi tidak berbeza bagi kumpulan fibrilasi atrium. Dos warfarin juga didapati

berbeza di antara kumpulan pemindahan injap aorta dan fibrilasi atrium untuk 5 minggu pertama permulaan terapi warfarin. Indikasi (p=0.036) dan kaum (p=0.016) didapati mempengaruhi dos warfarin dalam fasa permulaan terapi warfarin tetapi jantina (p=0.122) dan umur (p=0.280) didapati tidak mempunyai pengaruh penting. Secara keseluruhan, dos warfarin yang diperlukan di Hospital Pulau Pinang adalah lebih rendah berbanding dengan Negara Barat. Pemonitoran harus lebih kerap terhadap pesakit pemindahan injap jantung bagi tiga bulan pertama dalam fasa permulaan terapi warfarin.

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ABSTRACT

The use of warfarin is essential in patients having atrial fibrillation (AF), aortic valve replacement (AVR) and mitral valve replacement (MVR). However, the use of warfarin may bring major adverse effects such as bleeding and it has dose related side effects. Due to higher incidence of bleeding in initial phase of warfarin therapy and reported fluctuation of dose in initial phase of warfarin therapy after heart valve surgery, this study was conducted to evaluate the changes in warfarin doses among patients after heart valve surgery and atrial fibrillation. All patients having atrial fibrillation, aortic valve replacement and mitral valve replacement who were initiated warfarin therapy in year 2008 till 2010 in Hospital Pulau Pinang was selected as samples. A total of 137 patients were included for this study. Data collected included patient's age, race, gender, warfarin initiation date, warfarin indication, warfarin dose and INR value for 1st till 12th weeks of warfarin initiation. Statistical analysis was performed using repeated measures ANOVA and repeated measures ANCOVA. Heart valve replacement patients (AVR or MVR) showed increasing trend in warfarin doses during the initial phase of warfarin therapy. This trend was not observed in AF patients. The dose of warfarin was significantly different within first 12 weeks of warfarin initiation for AVR and MVR group (p-value <0.001) but there was no significant difference in AF group. The dose of warfarin was significantly different among AVR and AF patients for first 5 weeks of warfarin initiation. Indications (p-

value =0.036) and race (p-value =0.016) were found to be significantly affecting warfarin doses in the initial phase of warfarin therapy but not gender (p-value =0.122) and age (p-value =0.280). Overall, the mean dose of warfarin required was lower compared to western countries. Monitoring should be frequent for patients with heart valve replacement during the initial 3 months period of warfarin therapy.

CHAPTER 1

INTRODUCTION

1.1 Warfarin – history of drug development

The history of warfarin can be traced to the story of dairy farming in the Midwestern United States. In the early 1920s, there was an outbreak of a previously unrecognized disease of cattle, where cattle would die of uncontrollable bleeding. In 1922, Frank Schofield, a Canadian veterinarian identified that the cattle were ingesting a toxin from moldy silage made from sweet clover that functioned as a potent anticoagulant. In 1940, Karl Link and Harold Campbell, chemists at the University of Wisconsin, determined that it was coumarin derivative 4-hydroxycourmarin. In 1948, Link developed a more potent coumarin based anticoagulant – warfarin. (Dharmananda, 2004)

Warfarin was initially marketed as pesticide against rats and mice in the United States of America in 1952. Studies began in the use of warfarin as a therapeutic anticoagulant after a naval enlisted man unsuccessfully attempted suicide with warfarin bet recovered fully in 1951. In 1954, Warfarin was approved for medical use in humans (Dharmananda, 2004).

Almost 20 million prescriptions are written for warfarin each year in the US and it is one of the most challenging drugs in the modern medical formulary (Jonas and

McLeod, 2009). In Malaysia, warfarin remained the mainstay of the Vitamin K antagonist group, with about 0.05% of the population in Malaysia use warfarin everyday in a year (Sameerah and Sarojini, 2007).

1.2 Adverse effects of warfarin

The major adverse effect of warfarin is bleeding (Gallus *et al.*, 2000, Chai and Macik, 2002, Hirsh *et al.*, 2003, Pineo and Hull, 2003, Haines *et al.*, 2008). Major bleeding has been reported in 1.1% to 8.1% of patients during each year of long-term warfarin therapy, 1.1% to 2.7% by anticoagulant clinics managing patients with prosthetic heart valves, 1.3% in atrial fibrillation trials and 2.8 to 8.1% after a stroke or transient ischaemic attack (Gallus *et al.*, 2000. Intracerebral hemorrhage (ICH) is the most serious complication of oral anticoagulant therapy (OAT). The growing use of OAT has resulted in an increase of fatal ICH. The mortality rate is about 65%, and most of the surviving patients remain disabled (Huttneer *et al.*, 2006).

The intensity of International Normalized Ratio (INR) is the most important factor influencing bleeding risk (Gallus *et al.*, 2000, Pineo and Hull, 2003, Haines *et al.*, 2008). Other risk factors include old age, serious illness (cerebral, cardiac, kidney or liver disease), drug-drug interaction or cerebrovascular disease (Gallus *et al.*, 2000, Pineo and Hull, 2003, Haines *et al.*, 2008). Besides, poorer patients' knowledge about warfarin and lack of education are also associated with worse anticoagulation control and increased the frequency of hemorrhagic events (Fang *et al.*, 2006).

There are also others adverse effects associated with warfarin which included skin necrosis, osteoporosis and gastrointestinal side effects but these are uncommon (Haines *et al.*, 2008).

1.3 Problem associated with warfarin in the initiation phase

The therapeutic index of warfarin is narrow in any patient (Haines *et al.*, 2008) and patient's response to warfarin is highly variable. The dose requirement of warfarin can varies more than 10-fold between patients (Takahashi *et al.*, 2003, Hall and Wilkins, 2005). Age, weight, dietary intake of vitamin K, concurrent medication, gender, liver disease, congestive heart failure, serum albumin and Cytochrome P450 polymorphism, alcohol intake and patient's compliance contributed to the variation of the warfarin dose among patients (Wadelius *et al.*, 2004, Hall and Wilkins, 2005, Lee *et al.*, 2005).

The period of highest risk of bleeding complications is around the initiation of warfarin treatment (Douketis *et al.*, 2000, Kulik *et al.*, 2006). The risk of thromboembolic events is higher in the early 3 month compared to versus late postoperative phase. The challenge of initiation of warfarin will be to balance the risks of under-anticoagulation (thromboembolic events) against those of over-anticoagulation (bleeding complications), when the risk of bleeding may be significant in the initiation of treatment (Kulik *et al.*, 2006). Lowest yet adequate intensity of anticoagulation is important to minimize the risk of bleeding (Fuster *et al.*, 2001). The sensitivity to warfarin decreases after the initial period and the progressive decrease in warfarin sensitivity over several months often cause difficulty

to reach and maintain a stable International Normalized Ratio (INR) within therapeutic range (Rahman *et al.*, 2006, Meijer *et al.*, 2009).

1.4 Rational of the Study

Previous studies did not provide statistical approach to conclude whether the doses of warfarin would change after the initiation of warfarin therapy after aortic valve replacement, mitral valve replacement or atrial fibrillation (Meijer *et al.*, 2009). This study looked into the difference in warfarin doses after the initiation of warfarin therapy among patients with aortic valve replacement, mitral valve replacement or atrial fibrillation and also the differences between these 3 groups.

To researchers' knowledge, similar study had not been carried out in Malaysia. Studies from Western countries and North Asian countries may not be applicable to Malaysian population due to differences in geographical location and ethnic differences. Malaysia is a multiracial and multicultural country. Difference in races and lifestyle were known to be influential in warfarin dosing.

Moreover, this study also determined factors which associated with warfarin doses after the initiation of warfarin therapy among patients with aortic valve replacement, mitral valve replacement or atrial fibrillation. Therefore, the result of this study would help medical practitioner to recommend suitable doses of warfarin after the initiation of warfarin therapy among patients with aortic valve replacement, mitral valve replacement or atrial fibrillation.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of warfarin in valvular disease

Warfarin is prescribed to prevent thromboembolic complications after heart valve surgery (Kulik *et al.*, 2006). The risk of thromboembolism was highest in the first few months after surgery, both in mechanical and in bioprosthetic valves (Salem *et al.*, 2008). Current guidelines recommend anticoagulation for three months for a bioprosthetic valve, while for mechanical heart valves, lifelong anticoagulation is indicated (Salem *et al.*, 2008). In heart valves replacement, the decision regarding a mechanical versus bioprosthesis valve is based on factors like patient's age, overall longevity of the valve, relative contraindications to anticoagulation and lifestyle (Bonow *et al.*, 2008)

Atrial fibrillation is not considered as a lethal rhythm. However, it is known to exacerbate other existing cardiac conditions, such as heart failure and coronary artery disease, and is associated with increased risk for stroke (Chugh *et al.*, 2001). Warfarin is now widely used to prevent systemic embolism in otherwise healthy patients with atrial fibrillation (Gallus *et al.*, 2000). Warfarin is effective for prevention of systemic embolism in patients with nonvalvular atrial fibrillation (Hirsh *et al.*, 2003)

Generally, target INR for atrial fibrillation and heart valve replacement are 2.0-3.0 and 2.5-3.5 respectively (Hirsh *et al.*, 2003, Haines *et al.*, 2008). To be specific, in mechanical prostheses, target INR for first 3 months after replacement (for both AVR and MVR) will be 2.5-3.5 while for bioprostheses, target INR (for both AVR and MVR) in the initiation 3 months will be 2-3 (Bonow *et al.*, 2008, Salem *et al.*, 2008). Although warfarin is used for preventing and treating venous or arterial thromboembolism, it is a potentially hazardous drug (Gallus *et al.*, 2000). Each year, 1%-2% of patients treated with warfarin suffered from major bleeding, and about 0.1%-0.5% had intracranial bleeding (Gallus *et al.*, 2000).

Suboptimal anticoagulation therapy is a significant problem because it may lead to hemorrhagic and thromboembolic events (Heneghan *et al.*, 2010) Achieving therapeutic effectiveness and optimal outcomes for patients receiving warfarin remains complex. It is often a challenge to health care providers because of the influence of genomics, co morbidities, patient's age, additional prescription and / or over the counter medications, herbal products, dietary variability (eg: Vitamin K intake, anorexia), medication compliance and metabolic states (eg: fever, thyroid conditions) (Chai and Macik, 2002). Dosing schedules may be complex with frequent changes due to impact of diet, illness, and other medications on warfarin absorption and metabolism (Mazor *et al.*, 2007).

The INR is a good indicator of effectiveness and risk of bleeding during warfarin therapy (Gallus *et al.*, 2000). The risk of hemorrhage must always be weighed against the prevention of thromboembolism (Horton and Bushwick, 1999).

In order to minimize the adverse effects and achieving optimal clinical outcomes, there is a need to assess factors that affect warfarin dose in atrial fibrillation, aortic valve replacement and mitral valve replacement patients and the doses required to achieve desired therapeutic outcomes. This is particularly important in the initiation phase of warfarin therapy, since patients with heart valve replacement have an increase incidence of cardiac embolic events, particularly in the immediate postoperative period (Laffort *et al.*, 2000). The peak incidence of thromboembolism is during the first 3 months after surgery (Bonow *et al.*, 2008)

2.2 Heart valve replacement

There are four valves in the heart: aortic valve, mitral valve, tricuspid valve and pulmonary valve. Implantation of prosthetic cardiac valves was used to treat hemodynamically significant valvular disease. Since early 1960s, introduction of valve replacement surgery dramatically improved the outcome of patient with valvular heart disease (Pibarot and Dumesnil, 2009). Prosthetic valves are either created from synthetic material (mechanical valves) or fashioned from biological tissue (bioprosthetic valves) (Pibarot and Dumesnil, 2009).

Implantation of prosthetic valves put patient at risk of thrombocembolic complication and prosthetic valve thrombosis remains a serious and potentially lethal complication (Charokopos *et al.*, 2009, Pibarot and Dumesnil, 2009). The risk of thromboembolic events is higher with mechanical than with bioprosthetic valves. The risk of thromboembolic events is also higher with mitral valve replacement than with aortic valve replacement. Besides, the risk of thromboembolic events is higher in the early

(< 3 months) versus late postoperative phase (Chesebro and Fuster, 1996, Butchart *et al.*, 2002, Bonow *et al.*, 2008).

The early thromboembolic risk associated with the placement of a mechanical prosthesis depends on the complex interactions between the valve and recipient, the intrinsic thrombogenic properties of the mechanical valves components and the diligent management of post-operative anticoagulation (Kulik *et al.*, 2006). Standard of care after placement of mechanical valves is the utilization of oral anticoagulation (Kulik *et al.*, 2006).

Lifelong anticoagulation is needed in patient with mechanical prostheses while warfarin therapy is generally recommended during the first 3 months after implantation for patient with bioprostheses (Bonow *et al.*, 2008).

2.3 Atrial fibrillation (AF)

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function (Fuster *et al.*, 2001). Current understanding of the pathophysiology and epidemiology of AF is based primarily on studies in white populations of European ancestry with limited data on the non-white populations (Benjamin *et al.*, 2009).

The incidence of atrial fibrillation approximately doubles with each decade of adult life and ranges from 2 or 3 new cases per 1000 population per year between the ages of 55 and 64 years to 35 new cases per 1000 population per year between the ages of

85 and 94 years (Falk, 2001). There is limited information regarding AF incidence in Hispanic and Asian populations (Freestone *et al.*, 2003, Soliman *et al.*, 2009).

Meta-analysis of data from seven randomized clinical trials that prospectively collected information on the development of AF showed that Asians experiencing acute ischemic syndromes have a significantly lower frequency of AF compared with whites (Novaro *et al.*, 2008). The prevalence of AF was 2.8% among acute medical admissions to a single centre in Malaysia (Freestone *et al.*, 2003). However, the data are difficult to extrapolate to the general Malaysian population due to selection bias.

Stroke and systemic thromboembolism are serious problems for patients with AF (Soliman *et al.*, 2009). The major issues in management of patients with AF are related to the arrhythmia itself and the prevention of thromboembolism and stroke (Fuster *et al.*, 2001). The target intensity of anticoagulation has to balance between prevention of ischemic stroke and avoidance of hemorrhagic complications. It is important to target the lowest adequate intensity of anticoagulation to minimize the risk of bleeding, particularly for elderly patient with AF (Fuster *et al.*, 2001).

Warfarin should be given for 3 weeks before cardioversion and 4 weeks after successful cardioversion. However, patients with persistent or recurrent AF should be given chronic warfarin for stroke prevention and it is the preferred agent in patients at high risk of stroke (previous stroke, age over 75 years old, and/or poor left ventricular function) (King *et al.*, 2002).