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The Initiation Phase of Warfarin Therapy: Differences of Dose among Patients with Aortic Valve Replacement, Mitral Valve Replacement and Atrial Fibrillation

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ABSTRACT

This study was conducted to evaluate the changes in warfarin doses among patients after heart valve surgery and atrial fibrillation. A total of 137 patients having AF, AVR and MVR whom initiate warfarin therapy in year 2008 till 2010 in Penang Hospital were selected as samples 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. 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 ($p<0.001$) 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. Monitoring should be frequent for patients with heart valve replacement during the initial 3 months period of warfarin therapy.

INTRODUCTION

Warfarin, an oral anticoagulant, is widely used for preventing and treating vascular and thromboembolic disease (Haines *et al.,* 2008). 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 used warfarin everyday in a year (Sameerah and Sarojini, 2007). 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 vary more than 10-fold between patients (Hall and Wilkins, 2005; Takahashi *et al.,* 2003). 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 (Hall and Wilkins, 2005; Lee *et al.,* 2005; Wadelius *et al.,* 2004). 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 months) 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 adequate intensity of anticoagulation is important to minimize the risk of bleeding (Fuster *et al.,* 2001). The sensitivity to warfarin decrease after the initial period and the progressive decrease in warfarin sensitivity over several months often cause difficulty to reach and maintain a stable INR within therapeutic range (Meijer *et al.,* 2009; Rahman *et al.,* 2006).

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This study looked into the difference in warfarin doses after the initiation of warfarin therapy among patients with aortic valve replacement (AVR), mitral valve replacement (MVR) or atrial fibrillation (AF) and also between these three groups. To our knowledge, similar study has not been carried out in Malaysia. Studies from Western countries and north Asia countries may not be applicable to Malaysian population due to differences in geographical area and ethnicity. Malaysia is a multiracial and multicultural country. Difference in races and lifestyle were known to be influential in warfarin dosing. The aim of the study was to compare the warfarin doses differences in initial phase of warfarin therapy among patients with aortic valve replacement, mitral valve replacement and atrial fibrillation.

MATERIAL AND METHODS

Study Design and Participants

A retrospective record review study was conducted at warfarin clinic of Hospital Penang. The warfarin clinic was established in year 2008 for the patients from cardiothoracic and cardiology clinic. Patients from Cardiothoracic and Cardiology clinic who are on warfarin therapy were referred to this clinic for review and management. The source population was patients having atrial fibrillation, aortic valve replacement and mitral valve replacement who initiate warfarin therapy in year 2008 till 2010 in Penang Hospital. The sampling frame was patients having atrial fibrillation, aortic valve replacement and mitral valve replacement who initiated warfarin therapy in year 2008 till 2010 in Penang Hospital who fulfilled inclusion and exclusion criteria.

Patient who had INR within therapeutic range and who was having warfarin treatment after heart valve surgery or atrial fibrillation and follow up full 3 months in Penang General Hospital after heart valve surgery or atrial fibrillation were the inclusion criteria (Salem *et al.,* 2008). The exclusion criteria were atrial fibrillation patient who had undergone cardiac surgery 3 months before starting warfarin and patient having double valve replacement (Meijer *et al.,* 2009).

Case Definitions

Warfarin dose was defined as dose of warfarin in mg per day. Initial phase of warfarin therapy was defined as the first three months from starting the warfarin therapy. Dose of warfarin at Week 1 was defined as dose of warfarin in mg per day at the last day of the first week after patient's initiation of warfarin therapy. Data collected included patient's age, race, gender, warfarin initiation date, warfarin indication, INR value and twelve readings of warfarin dose for 1st till 12th weeks of warfarin initiation.

Statistical Analysis

All statistical analysis was performed using SPSS software version 17. Baseline characteristics were presented in frequencies and percentages or were expressed as mean and standard deviation. These included indication, age, race and gender. One-way repeated measures ANOVA and multi-way repeated measures ANCOVA analysis was used to evaluate the significance of difference between groups and among groups. Three types of effect were analyzed using one-way repeated measures ANOVA model. These effects were within warfarin indication group (Time effect), between warfarin indication groups (Group effect) and within-between design (Time-Group Interaction). Multi-way repeated measures ANCOVA analysis was used to analyze between warfarin indication groups effect (Group effect) and within-between design (Time-Group Interaction) after controlled age, gender and race. Three assumptions were tested for one-way repeated measures ANOVA and multi-way repeated measures ANCOVA analysis. First, the assumption of normality was tested. All 12 residuals were checked by using histogram and box and whisker plot. Second, the assumption of homogeneity of variances was tested by using Levene's test of Equality of Error Variances and observations in the scatter plots of all twelve residual vs predicted values. Third, the assumption of compound symmetry was tested by using Mauchly's test of sphericity. Results were considered significant at a 95% level of confidence.

Ethical Approval

The study received approval from The Research Ethics Committee (Human) of Universiti Sains Malaysia (USMKK/PPP/JEPeM[230.4(1.1)] and Medical Research and Ethics Committee (MREC) of Ministry of Health Malaysia (NMRR-10-798-6522).

RESULTS

A total of 137 patients were included for this study. After data exploration, four samples out of 137 samples were excluded from analysis. These four samples were having very high warfarin doses (6mg or more) and their residual values were more than three. The four samples excluded were two AVR and two MVR. The two AVR samples excluded were two Indian male and the two MVR samples excluded were one Malay male and one Malay female. Among 133 patients selected for analysis. A total of 59 (44.4%) patients were female and 74 (55.6%) were male. Around 61 (45.9%) of them were atrial fibrillation patients, 28 (21.1%) had undergone aortic valve replacement and 44 (33.1%) had undergone mitral valve replacement. For the races composition, Chinese were the majority with 62 patients (46.6%), followed by Malay 56 patients (42.1%) and Indian 15 patients (11.3%). The mean age of the selected samples was 53.69 years with the standard deviation 15.52 (Table 1). Mean dose (SD) of warfarin for AF patients remained steady with a dose of near 3mg (2.83mg (0.81) in the first week to 2.98mg (0.93) in the twelfth week) throughout the first 3 months of therapy. Mean dose (SD) of warfarin for AVR patients steadily increased from 2.14mg (0.90) at first week of warfarin therapy to 2.96mg (0.89) at twelfth weeks of therapy. Mean dose (SD) of warfarin for AVR patients steadily increased from 2.14mg (0.90) at first week of warfarin therapy to 2.96mg (0.89) at twelfth weeks of therapy.

Table 1: Characteristics of patients selected as samples for the study (n=133).

Patient's Characteristic	n (%)
Gender	
Female	59 (44.4)
Male	74 (55.6)
Indication	
Atrial Fibrillation	61 (45.9)
Aortic Valve Replacement	28 (21.1)
Mitral Valve Replacement	44 (33.0)
Race	
Malay	56 (42.1)
Chinese	62 (46.6)
Indian	15(11.3)

For comparison of warfarin doses in initiation phase among patients with aortic valve replacement and mitral valve replacement (within group), the Mauchly's test of sphericity is significant (p-value <0.05) which means the assumption of compound symmetry was not met. Therefore, epsilon correction was used. By using epsilon correction, within group's difference was found significant (p-value < 0.05). Multiple paired T test was carried out for all possible pairs in three different groups (AF, AVR and MVR). A total of 66 pairs for each group were compared. Bonferroni correction was performed due to the multiple paired comparisons. Since there are 66 comparisons for each group, significance level for each comparison was set at 0.05 / 66 = 0.0008. Therefore, p-value that <0.001 was considered significant. From multiple paired T test, within group differences were found significant (p-value <0.001 after bonferroni correction) in AVR group and MVR group. There was no significant different within group in the AF group (Table 2).

Table 2: Comparison of warfarin doses within each group (indication) (n=133)

Week	Atrial Fibrillation		Aortic valve replacement		Mitral valve replacement	
	Mean Diff.	P-value	Mean Diff.	P-value	Mean Diff.	P-value
$1^{st} - 2^{nd}$	-0.066	0.209	-0.071	0.293	0.011	0.878
$1^{st} - 3^{rd}$	-0.082	0.221	-0.089	0.379	0.045	0.682
$1^{st} - 4^{th}$	-0.115	0.123	-0.054	0.656	0.045	0.675
$1^{st} - 5^{th}$	-0.172	0.030	-0.268	0.061	0.045	0.694
$1^{st} - 6^{th}$	-0.156	0.066	-0.464	0.003	-0.091	0.508
$1^{st} - 7^{th}$	-0.164	0.058	-0.571	0.002	-0.136	0.333
$1^{st} - 8^{th}$	-0.148	0.109	-0.625	0.001	-0.216	0.128
$1^{st} - 9^{th}$	-0.148	0.138	-0.710	< 0.001	-0.250	0.088
$1^{st} - 10^{th}$	-0.148	0.124	-0.768	< 0.001	-0.284	0.038
$1^{st} - 11^{th}$	-0.139	0.145	-0.786	< 0.001	-0.364	0.010
$1^{st} - 12^{th}$	-0.148	0.132	-0.821	< 0.001	-0.466	0.001
$2^{nd} - 3^{rd}$	-0.016	0.621	-0.018	0.713	0.034	0.660
$2^{nd} - 4^{th}$	-0.049	0.242	0.018	0.839	0.034	0.706
$2^{nd} - 5^{th}$	-0.107	0.036	-0.196	0.102	0.034	0.730
$2^{nd} - 6^{th}$	-0.090	0.117	-0.393	0.005	-0.102	0.335
$2^{nd} - 7^{th}$	-0.098	0.109	-0.500	0.003	-0.148	0.199
$2^{nd} - 8^{th}$	-0.082	0.221	-0.554	0.001	-0.227	0.053
$2^{nd} - 9^{th}$	-0.082	0.261	-0.643	0.001	-0.261	0.033
$2^{nd} - 10^{th}$	-0.082	0.255	-0.696	< 0.001	-0.295	0.008
$2^{nd} - 11^{th}$	-0.074	0.303	-0.714	< 0.001	-0.375	0.001
$2^{nd} - 12^{th}$	-0.082	0.267	-0.750	< 0.001	-0.477	< 0.001
$3^{rd} - 4^{th}$	-0.033	0.209	0.036	0.602	0.000	1.000
$3^{rd} - 5^{th}$	-0.090	0.015	-0.179	0.086	0.000	1.000
$3^{rd} - 6^{th}$	-0.074	0.107	-0.375	0.004	-0.136	0.044
$3^{rd} - 7^{th}$	-0.082	0.105	-0.482	0.002	-0.182	0.025
$3^{rd} - 8^{th}$	-0.066	0.251	-0.536	0.001	-0.261	0.002
$3^{rd} - 9^{th}$	-0.066	0.289	-0.625	< 0.001	-0.295	0.001
$3^{rd} - 10^{th}$	-0.066	0.289	-0.679	< 0.001	-0.330	< 0.001
$3^{rd} - 11^{th}$	-0.057	0.349	-0.696	< 0.001	-0.409	< 0.001
$3^{rd} - 12^{th}$	-0.066	0.306	-0.732	< 0.001	-0.511	< 0.001
$4^{th} - 5^{th}$	-0.057	0.034	-0.214	< 0.001	0.000	1.000
$4^{th} - 6^{th}$	-0.041	0.255	-0.411	< 0.001	-0.136	0.038
$4^{th} - 7^{th}$	-0.049	0.242	-0.518	< 0.001	-0.182	0.025
$4^{th} - 8^{th}$	-0.033	0.497	-0.571	< 0.001	-0.261	0.002
$4^{th} - 9^{th}$	-0.033	0.532	-0.661	< 0.001	-0.295	0.001
$4^{th} - 10^{th}$	-0.033	0.532	-0.714	< 0.001	-0.330	< 0.001
$4^{th} - 11^{th}$	-0.025	0.635	-0.732	< 0.001	-0.409	< 0.001
$4^{th} - 12^{th}$	-0.033	0.542	-0.768	< 0.001	-0.511	< 0.001
$5^{th} - 6^{th}$	0.016	0.484	-0.196	0.003	-0.136	0.013
$5^{th} - 7^{th}$	0.008	0.784	-0.304	0.002	-0.182	0.010
$5^{th} - 8^{th}$	0.025	0.517	-0.357	0.001	-0.261	0.001
$5^{th} - 9^{th}$	0.025	0.568	-0.446	< 0.001	-0.295	0.001
$5^{th} - 10^{th}$	0.025	0.568	-0.500	< 0.001	-0.330	< 0.001
$5^{th} - 11^{th}$	0.033	0.454	-0.518	< 0.001	-0.409	< 0.001
$5^{th} - 12^{th}$	0.025	0.594	-0.554	< 0.001	-0.511	< 0.001
$6^{th} - 7^{th}$	-0.008	0.658	-0.107	0.110	-0.045	0.160
$6^{th} - 8^{th}$	0.008	0.766	-0.161	0.026	-0.125	0.015
$6^{th} - 9^{th}$	0.008	0.811	-0.250	0.011	-0.159	0.015
$6^{th} - 10^{th}$	0.008	0.821	-0.304	0.002	-0.193	0.006
$6^{th} - 11^{th}$	0.016	0.658	-0.321	0.001	-0.273	< 0.001
$6^{th} - 12^{th}$	0.008	0.837	-0.357	0.001	-0.375	< 0.001
$7^{th} - 8^{th}$	0.016	0.419	-0.054	0.083	-0.080	0.033
$7^{th} - 9^{th}$	0.016	0.597	-0.143	0.030	-0.114	0.031
$7^{th} - 10^{th}$	0.016	0.621	-0.196	0.005	-0.148	0.014
$7^{th} - 11^{th}$	0.025	0.471	-0.214	0.005	-0.227	0.001
$7^{th} - 12^{th}$	0.016	0.641	-0.250	0.002	-0.330	< 0.001
$8^{th} - 9^{th}$	0.000	1.000	-0.089	0.134	-0.034	0.183
$8^{th} - 10^{th}$	0.000	1.000	-0.143	0.030	-0.068	0.083
$8^{th} - 11^{th}$	0.008	0.766	-0.161	0.026	-0.148	0.001
$8^{th} - 12^{th}$	0.000	1.000	-0.196	0.009	-0.250	< 0.001
$9^{th} - 10^{th}$	0.000	1.000	-0.054	0.083	-0.034	0.262
$9^{th} - 11^{th}$	0.008	0.568	-0.071	0.043	-0.114	0.006
$9^{th} - 12^{th}$	0.000	1.000	-0.107	0.011	-0.216	0.001
$10^{th} - 11^{th}$	0.008	0.321	-0.018	0.326	-0.080	0.007
$10^{th} - 12^{th}$	0.000	1.000	-0.054	0.083	-0.182	0.002
$11^{th} - 12^{th}$	-0.008	0.321	-0.036	0.161	-0.102	0.048

*multiple paired t test with 66 comparisons

*Bonferroni correction applied, significance level = 0.05 / 66 =0.0008

For comparison of warfarin doses in initiation phase between patients with AF, AVR and MVR, analysis were performed using one-way repeated measures ANOVA and multi-way repeated measures ANCOVA. Both analyses showed that the dose of warfarin was significantly different for AVR and AF in the first 5 weeks by comparing their 95% confidence interval respectively after controlled age, gender and race. In the first 5 weeks, the upper limit and lower limit of AVR group did not overlap with upper limit and lower limit of AF group (Table 3).

In one-way repeated measures ANOVA, indications (AF, AVR and MVR) were found not significantly different in warfarin doses regardless of time with the p-value 0.143. Post-hoc test showed that the mean difference between these 3 indications are not significant (p-value >0.05) (Table 4). However, Indications (AF, AVR and MVR) were found significantly different in warfarin doses regardless of time with the p-value 0.036 when age, gender and race were controlled using multi-way repeated measures ANCOVA. Post-hoc test was carried out by comparing the estimated marginal means with using Sidak method to adjust for multiple comparisons. Sidak method was chosen because we assumed that the individual tests are independent. The significant difference of warfarin doses occurred between AF group and AVR group with the p-value of 0.03.

Table 3: Comparison of warfarin doses among three different indication between one-way repeated measures ANOVA and multi-way repeated measures ANCOVA (n=133).

Time (week)	Groups	One-way repeated measures ANOVA		Multi-way repeated measures ANCOVA	
		Mean warfarin doses (mg)	95% CI	Mean warfarin doses (mg)	95% CI
1st	Atrial Fibrillation	**2.83**	**2.60,3.05**	**2.99**	**2.71,3.27**
	Aortic valve replacement	**2.14**	**1.81,2.48**	**2.13**	**1.75,2.51**
	Mitral valve replacement	2.60	2.34,2.87	2.74	2.41,3.07
2nd	Atrial Fibrillation	**2.89**	**2.67,3.12**	**3.10**	**2.83,3.37**
	Aortic valve replacement	**2.21**	**1.89,2.54**	**2.20**	**1.82,2.57**
	Mitral valve replacement	2.59	2.33,2.85	2.73	2.41,3.05
3rd	Atrial Fibrillation	**2.91**	**2.68,3.14**	**3.13**	**2.86,3.40**
	Aortic valve replacement	**2.23**	**1.90,2.57**	**2.24**	**1.87,2.62**
	Mitral valve replacement	2.56	2.29,2.82	2.73	2.41,3.05
4th	Atrial Fibrillation	**2.94**	**2.72,3.17**	**3.17**	**2.90,3.44**
	Aortic valve replacement	**2.20**	**1.87,2.53**	**2.16**	**1.79,2.53**
	Mitral valve replacement	2.56	2.29,2.82	2.70	2.38,3.02
5th	Atrial Fibrillation	**3.00**	**2.78,3.22**	**3.20**	**2.93,3.47**
	Aortic valve replacement	**2.41**	**2.08,2.74**	**2.43**	**2.05,2.80**
	Mitral valve replacement	2.56	2.29,2.82	2.73	2.40,3.05
6th	Atrial Fibrillation	2.98	2.76,3.21	3.15	2.87,3.44
	Aortic valve replacement	2.61	2.27,2.95	2.59	2.20,2.98
	Mitral valve replacement	2.69	2.42,2.96	2.88	2.54,3.22
7th	Atrial Fibrillation	2.99	2.75,3.23	3.17	2.88,3.47
	Aortic valve replacement	2.71	2.36,3.07	2.68	2.27,3.09
	Mitral valve replacement	2.74	2.46,3.02	2.91	2.55,3.26
8th	Atrial Fibrillation	2.98	2.73,3.21	3.14	2.84,3.45
	Aortic valve replacement	2.77	2.41,3.13	2.71	2.29,3.14
	Mitral valve replacement	2.82	2.53,3.10	2.98	2.61,3.34
9th	Atrial Fibrillation	2.98	2.73,3.23	3.18	2.87,3.49
	Aortic valve replacement	2.86	2.49,3.23	2.77	2.34,3.20
	Mitral valve replacement	2.85	2.56,3.15	3.00	2.63,3.38
10th	Atrial Fibrillation	2.98	2.73,3.22	3.17	2.87,3.48
	Aortic valve replacement	2.91	2.49,3.23	2.82	2.40,3.24
	Mitral valve replacement	2.89	2.60,3.17	3.02	2.66,3.38
11th	Atrial Fibrillation	2.97	2.72,3.21	3.18	2.87,3.48
	Aortic valve replacement	2.93	2.57,3.29	2.84	2.42,3.26
	Mitral valve replacement	2.97	2.68,3.25	3.09	2.72,3.45
12th	Atrial Fibrillation	2.98	2.73,3.22	3.19	2.88,3.51
	Aortic valve replacement	2.96	2.60,3.33	2.87	2.43,3.30
	Mitral valve replacement	3.07	2.78,3.36	3.16	2.79,3.53

* Age, gender and race were controlled under multi-way repeated measures ANCOVA

Table 4: Comparison of mean difference of warfarin doses among three different indications regardless of time (n=133)

Compare	One-way RM ANOVA		Multi-way RM ANCOVA[b]	
	Mean Difference[a] (95% CI)	P-value	Mean Difference[c] (95% CI)	P-value
Atrial Fibrillation – Aortic valve replacement	0.373 (-0.114,0.859)	0.170	0.613 (0.045,1.182)	0.030
Atrial Fibrillation – Mitral valve replacement	0.211 (-0.211,0.633)	0.466	0.260 (-0.270,0.790)	0.555
Aortic valve replacement –Mitral valve replacement	-0.162 (-0.677,0.354)	0.740	-0.353 (-0.239,0.946)	0.389

[a] Scheffe test was used as post-hoc test
[b] Age, gender and race were controlled
[c] Adjustment for multiple comparisons: Sidak

DISCUSSION

The mean warfarin dose in this study was lower than the results from Meijer *et al* where they reported the mean warfarin dose of warfarin for mechanical valve replacement patients steadily increased from 3.79 mg to 4.37 mg at first week and thirteenth week respectively (Meijer *et al*., 2009). Similarly, the mean warfarin dose in the study also lower as compared to results from Mesbah Rahman *et al* where they reported the mean dose (SD) of warfarin increased from 3.55 mg (1.94) to 5.09 mg (2.03) at the first week and twelfth week respectively after heart valve replacement (Rahman *et al.,* 2006). The trend of lower mean warfarin dose in the study compared to the one reported in Western countries (Meijer *et al.,* 2009; Rahman *et al.,* 2006) was consistent with studies done by others Asian countries which showed Asian populations generally need lower dose of warfarin to achieved INR target (Jonas and McLeod, 2009; Mori *et al.,* 2002; Sun *et al.,* 2003; Yang *et al*., 2010; Zhou *et al.,* 2005). This

might due to genetic difference between Asian and Western population where Vitamin K epoxide reductase complex subunit 1 (VKORC1) genotype (known to affect warfarin sensitivity (Jonas and McLeod, 2009)) frequencies of Asian and Caucasian patients were different (Yang *et al.,* 2010). Besides, diet which was different between Asian and Western populations might also contributed to the difference in warfarin dose needed (Jonas and McLeod, 2009)

The mean warfarin dose in AVR and MVR patients after 3 months of therapy was 38.3% and 18.1% higher than first week of therapy. The result was consistent with study done by Mesbah Rahman *et al* and Meijer *et al*. In result reported by Mesbah Rahman *et al*, the dose requirement of warfarin after 3 months of therapy was 43% higher compared to first week of therapy (Rahman *et al*., 2006). For Meijer *et al*, the dose requirement of warfarin after 3 months of therapy was 26% higher compared to first week of therapy (Meijer *et al.,* 2009). However, Mesbah Rahman *et al* did not separate the dose increment in AVR and MVR group. Besides, Meijer *et al* did not include patients with MVR.

Results showed that warfarin requirements were in increasing trend during the first three months after heart valve replacement (both AVR and MVR) but this pattern was absent in patients with AF. The trend was consistent with previous studies (Meijer *et al.,* 2009; Rahman *et al*., 2006). Several factors might contribute to the increasing trend of mean warfarin dose among patients with AVR and MVR. Factors known to affect the warfarin sensitivity including recovery from hypoalbuminemia after surgery (Ageno and Turpie, 1999; Rahman *et al*., 2006), improvement in hepatic congestion and cardiac output (Rahman *et al.,* 2006), increase in dietary intake of vitamin K and decreasing adherence to therapy (Meijer *et al.*, 2009).

Hypoalbuminemia can affect the volume of distribution and half-life of warfarin since warfarin was almost 99% bound to albumin (Charles F. Lacy *et. al*, 2009). Hypoalbuminemia enhance the response of warfarin in postoperative cardiac surgical patients (Ageno and Turpie, 1999).

We could not trace the patients' serum albumin level in this study. However, except patients with some underlying diseases like persistent sepsis, hepatic impairment, nephrotic syndrome or hyperthyroidism that decreased synthesis, affect redistribution and increased loss or catabolism of albumin (Crook, 2009); it is unlikely that hypoalbuminemia levels would be persistent throughout the 3 months period. When patients recover from heart valve surgery, the improvement in albumin level would cause increment of the warfarin dose requirement in order to maintain the targeted INR. Nevertheless, it seems unlikely that the albumin level would steadily continue to increase over a period of three months (Meijer *et al.,* 2009). Therefore, improvement of albumin level might be the factor that caused the need to increase warfarin dose until patient achieved normal albumin level but not the increasing trend throughout the period of three months.

Among 3 different indication (AF, AVR and MVR), the dose of warfarin was significantly different for AVR and AF in the first 5 weeks. This might due to physiological changes after heart valve surgery as discussed before.

The targeted INR set for patients with AF, AVR and MVR was 2.0 - 3.0, 1.8 - 2.5 and 2.5 - 3.5 respectively in Hospital Penang. This might explain why there was no significant difference in the dose throughout the 3 months study period between patients with AF and MVR. Hypoalbuminemia, hepatic congestion and decreased in cardiac output might also cause the need of lower warfarin dose in MVR patients same as AVR patients in the early phase of post-surgery. However, as the targeted INR for MVR patients was higher compared to AVR patients, therefore a higher warfarin dose needed for MVR patients to achieve the higher targeted INR compared to AVR patients. As a result, there was no significant difference between mean warfarin dose in AF and MVR patients.

Our study was limited by retrospective study design. A few factors that found to be affecting warfarin doses could not be measured in our study as it was not recorded in patients' record. These included body mass index (BMI), body weight, valve type and compliance to medications. The unmeasured variables may have impact on warfarin doses in initial phase of warfarin therapy. Ratio composition for indications was not equal in our study. AVR patients were least recruited to this study due to lack of patients. Lack of samples for AVR patients may reduce the power of the study.

Since warfarin doses was in increasing trend and the dose was significantly different during the first three months of therapy in AVR and MVR patients, monitoring during the initial 3 months period should be frequent in these group of patients. It is likely that AVR and MVR patients require an increase in the warfarin dose in order to maintain the targeted INR to avoid thromboembolism event.

CONCLUSION

As conclusion, 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 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. Indication was found to be significantly affecting warfarin doses in the initial phase of warfarin therapy.

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