Assessment of the Clinical Outcomes of Warfarin Therapy in Two Models of Anticoagulation Services

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Abstract

Introduction: The quality of anticoagulation control is commonly expressed by time spent in the therapeutic international normalised ratio (INR) range (TTR). It is important to ensure the optimal outcome during therapy because the high variability of INR is associated with adverse outcomes.

Objective: This study was conducted to assess the clinical outcomes of warfarin therapy among warfarin treated patients in usual medical care (UMC) and Warfarin Medication Therapy Adherence Clinic (WMTAC) in Kajang Hospital.

Methods: A cross-sectional study of randomly sampled patients from UMC and WMTAC was carried out from May 2013 to May 2014. The primary outcomes were the percentage of time when INR was within the therapeutic range (% TTR) and the percentage of time when INR was within the expanded therapeutic range (% expanded TTR). The secondary outcomes were the number and severity of haemorrhagic and thromboembolic complications, and patients' compliance and defaulter rate.

Results: A total of 78 patients were recruited (45 patients in UMC and 33 patients in WMTAC). The most common indications for warfarin were atrial fibrillation and mechanical heart valves. The TTR was 66.6% for WMTAC and 45.5% for UMC patients ($p<0.001$) while the expanded TTR for WMTAC was 79% and 55.8% for UMC ($p<0.001$). There was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. The compliance score showed significant difference with WMTAC patients scored 1.45 and UMC patients scored 2.29. The defaulter rate was significantly lower in WMTAC (3%) compared to UMC (22%) ($p=0.038$).

Conclusion: The pharmacist-managed WMTAC can help patients to achieve better anticoagulation control, higher compliance to warfarin and lower defaulter rate among patients receiving warfarin therapy. Therefore, more cooperation between the physicians and pharmacists as such should be promoted to explore the potential to improve patient therapeutic outcomes.

Keywords: warfarin, anticoagulation care, warfarin therapy, pharmacist-managed warfarin clinics, medication therapy adherence clinic

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Introduction

Warfarin, a Vitamin K antagonist, is the most widely used anticoagulant in thromboembolic diseases prevention and treatment (1). Treatment with warfarin, however, is challenging due to its narrow therapeutic index, complicated pharmacokinetic and pharmacodynamic profiles as well as drug interactions (2). The quality of anticoagulation control is commonly expressed as the time spent in the therapeutic international normalised ratio (INR) range (TTR). It is important to ensure optimal TTR during therapy because the high variability of INR is associated with adverse outcomes such as thromboembolism and bleeding events (3).

There are two primary models available in Kajang Hospital for managing oral anticoagulation therapy: the physician-managed oral anticoagulation clinics which is the usual medical care (UMC) in most hospitals and the pharmacist-managed Warfarin Medication Therapy Adherence Clinic (WMTAC). WMTAC was introduced as a clinical pharmacy service in the ambulatory care. It serves to enhance patient care for patients on anticoagulation therapy through pharmacist counselling, patient education and close follow-up, thereby

optimising treatment benefits and minimising complications from anticoagulation therapy (4). Several studies found that pharmacist-managed warfarin therapy results in decreased warfarin-related hospital admission, less drug interactions as well as improved patient compliance and anticoagulation control (4-5). High-quality anticoagulant therapy could reduce thromboembolic events while minimising bleeding risk (6). In view of the lack of studies on the effects of pharmacist-managed anticoagulation clinics in our local settings, this study was conducted in Kajang Hospital, Malaysia to assess the clinical outcomes among warfarin treated patients. We compared coagulation control between UMC and WMTAC patients in terms of percentage of time when the INR was within the therapeutic range (% TTR), percentage of time when the INR was within the expanded therapeutic range (% expanded TTR) and the number and severity of haemorrhagic and thromboembolic events. This study also evaluated patients' compliance towards warfarin therapy and the rate of defaulter among warfarin treated patients in both groups.

Method

Usual medical care (UMC) and Warfarin Medication Therapy Adherence Clinic (WMTAC)

A cross-sectional study was carried out in the anticoagulation clinics in Kajang Hospital from May 2013 to May 2014. The anticoagulation clinics were categorized as UMC and WMTAC. UMC was the usual medical clinic managed by the physicians that operates for three days in a week. On the other hand, WMTAC is conducted by the pharmacists on a weekly basis. Patients under the regular follow-up of the UMC clinic will be referred to the WMTAC according to clinical needs.

Both clinics required the patients to have their blood drawn for an INR test during their follow up. The physicians and pharmacists will then assess patients' INR results. For the UMC group, dosage changes and time intervals for INR blood tests were at the discretion of the individual physician based on their knowledge and experience in the management of warfarin. There was no specific dosing guide for UMC.

The pharmacists involved in WMTAC are required to complete a two-week short course on anticoagulation management to equip themselves with the clinical knowledge to assess patients individually to develop patient-specific recommendations. The management of the warfarin therapy was carried out in accordance with the Ministry of Health (MOH) WMTAC Protocol (4). This protocol included evidence-based guidelines for dosage recommendations and intervals for INR testing The WMTAC pharmacists maintain a list of all the WMTAC patients and a record of patients scheduled for appointment. During the WMTAC appointment, patients were assessed for changes in their medications or diet, signs and symptoms of haemorrhagic or thromboembolic events, missed doses and illnesses. Besides playing an expanded role in patient education and counselling, pharmacists in the WMTAC use the MOH WMTAC Protocol guideline as well as clinical judgement to develop the care plan of dosage change if required. Assessment and recommendations made were documented into the patients' records, which were made available to the physicians. In cases where INR readings are less than 1.0 or more than 4.0, suspicion of serious adverse effects, new clots or serious bleeding, patients will be referred to physician as outlined in the protocol.

Ethical Considerations

Approval to conduct the study was obtained from the Ministry of Health Malaysia (MOH) Medical Research and Ethics Committee (MREC) and the study was registered with the National Medical Research Register (NMRR). Permission from the head of Medical Department was obtained to conduct the study. The patients who met the inclusion criteria were interviewed to assess their compliance. Prior to that, a consent requesting them to willingly participate in the study was obtained. Participants were explained the purpose of the study and assurance of anonymity in the management of data. In addition, they were allowed to ask questions about the interviews. All data collection and information were remained confidential according to the ethical requirements.

Study Population

Eligible patients were screened for recruitment based on inclusion criteria which were adults aged 18 years and above, on warfarin therapy for at least 3 months and under follow up of anticoagulation clinics for at least 3 months. There should be at least two INR readings taken not more than 6 weeks apart. Patients taking warfarin for antiphospholipid syndrome were not included in this study. INR readings taken during hospitalization and during temporary planned interruptions were excluded. It was predicted that the physician-managed

anticoagulation service in UMC would achieve the target INR in about 50% of the time (9-10). Hence, a sample size of 45 patients in each group would be required to have a statistical power of 80% and α error of 0.05 to detect the difference.

Study Outcomes

The primary outcomes were the percentage of TTR and expanded TTR of patients in the WMTAC group compared to the UMC group. The percentage of time patients' INR in therapeutic range reflects INR control over time. The percentage was obtained by dividing the number of INRs within the target range for each patient with the overall number of INRs during that selected time interval. The expanded therapeutic INR range was defined as the therapeutic range INR ±0.2, where dosage adjustment is not required because such variation is not considered clinically significant (1). Thus, the percentage of TTR and expanded TTR of patients were calculated using equation, as follows:

$$\% \text{ TTR} = \frac{\text{Number of INR within the target range}}{\text{Total number of INR}} \times 100$$

$$\% \text{ expanded TTR} = \frac{\text{Number of INR within the } \pm 0.2 \text{ target range}}{\text{Total number of INR}} \times 100$$

The secondary outcome measurement included adverse events or complications, patients' compliance and defaulter rate. Thromboembolic and haemorrhagic adverse events are possible complications of warfarin adverse events. Thromboembolic event is defined as any embolic or thrombotic cerebrovascular accident, deep vein thrombosis, pulmonary embolism or other systemic thromboembolic events detected during the study period. Cases which do not require hospitalisation were classified as minor events whereas those require hospitalisation were classified as major events. Major bleeding was defined as bleeding episode which requires hospitalisation whereas minor bleeding does not require further intervention. Minor bleeding includes mild bruising, nose bleeding, gum bleeding, haematuria and rectal bleeding (7).

Warfarin Compliance-Assessment Scale (WCAS) developed by Huber *et al*. from the Community Anticoagulation Therapy Clinic was used to measure the patient's compliance towards warfarin therapy. It is a compliance tool that assigns points to the various aspects of medication use, diet, and alcohol use. The tool provides an objective measure of patient compliance with warfarin therapy. Lower score indicates higher compliance (8). On the other hand, rate of defaulter is defined as the percentage of scheduled appointments defaulted by patients during the study period. The percentage was obtained by dividing the number of appointments missed by patients with the total number of appointments made by UMC or WMTAC during the study period.

Data Collection

Simple random sampling technique was used to recruit sample in this study. Since the hospital does not have a computerized data system, the list of patients who were on warfarin therapy was captured manually from the patients' medical files and prescriptions. The patients who met the inclusion criteria were interviewed to assess patients' compliance using WCAS. In addition, a data collection form was used to extract data from patients' medical records, which include patients' demographics, medical illness, indications for warfarin, INR target, duration of therapy, risk factors for bleeding or thromboembolic events, concurrent medication, occurrence of haemorrhagic and thromboembolic complications after initiation of warfarin as well as the number of appointments made and missed during the study period.

Statistical analysis

Statistical analysis was performed using SPSS version 20. Descriptive statistics was used to describe the demographic characteristics of the patients. For INR control, the mean and standard deviation (SD) value for the percentage days in range was calculated for all the patients who were included for INR control analysis. The default rate, % TTR and % expanded TTR were analyzed using independent t-test with 0.05 set as the level of significance. The differences in complications and compliances between the two groups were analyzed using Chi-square test.

Results

For UMC group, 63 out of 102 patients screened met the inclusion criteria. Out of 63 patients, 45 patients were randomly selected. Out of 43 WMTAC patients screened, 33 patients who met the inclusion criteria were included, making a total of 78 patients in the study. The demographic data showed that the baseline characteristics were similar between the groups. The majority of the warfarin treated patients were male (45.5% in WMTAC and 64.4% in UMC) and Malay (60.6% in WMTAC and 55.6% in UMC). The most common indications for warfarin were atrial fibrillation (AF) and mechanical heart valves. Of the 78 patients recruited, three patients had individually narrowed INR targets, i.e. 2.0 to 2.5 and 2.5 to 3.0.

Table 1: Demographic characteristics of the study population (n=78)

Variables	WMTAC, n (%)	UMC, n (%)	X^2-stats (df)	P-value
Gender			2.792 (1) [a]	0.09
Male	15 (45.5)	29 (64.4)		
Female	18 (54.5)	16 (35.6)		
Age			7.083 (5) [b]	0.214
31-40	1 (3.0)	1 (2.2)		
41-50	6 (18.2)	5 (11.1)		
51-60	3 (9.1)	17 (37.8)		
61-70	8 (24.2)	11 (24.4)		
71-80	11 (33.3)	9 (20.0)		
81-90	4 (12.1)	2 (4.4)		
Race			0.483 (2) [a]	0.785
Malay	20 (60.6)	25 (55.6)		
Chinese	9 (27.3)	12 (26.7)		
India	4 (12.1)	8 (17.8)		
Warfarin indication			0.643 (6) [b]	0.996
AF	23 (69.7)	31 (68.9)		
Mechanical heart valve	6 (18.2)	5 (11.1)		
AF & MVR	2 (6.1)	1 (2.2)		
DVT	0	2 (4.4)		
PE	0	1 (2.2)		
MI/ACS	0	1 (2.2)		
Others	2 (6.1)	4 (8.9)		
Risk factors for thromboembolism or bleeding			8.183 (4) [b]	0.085
Hypertension	19 (57.6)	12 (26.7)		
Diabetes mellitus	3 (9.1)	1 (2.2)		
Previous cardiovascular accident	0	1 (2.2)		
Hypertension & Diabetes mellitus	2 (6.1)	10 (22.2)		
Nil	9 (27.3)	21 (46.7)		
INR range target			1.182 (3) [b]	0.757
2.0-3.0	25 (76)	40 (89)		
2.0-2.5	1 (3)	1 (2)		
2.5-3.0	1 (3)	0		
2.5-3.5	6 (18)	4 (9)		

[a] Chi-square test; [b] Chi-square test (Yate's)
Abbreviation: AF – atrial fibrillation; MVR – mechanical valve replacement; DVT – deep vein thrombosis; PE – pulmonary embolism; MI – myocardial infarct; ACS – acute coronary syndrome

Table 2 summarised the anticoagulation control of WMTAC and UMC patients. The frequency of INR assessment was significantly higher in WMTAC patients, with mean 12 (SD 2.9) INR assessments per patient, compared to UMC patients who had mean 7.7 (SD 3) INR assessments per patient over 12 months ($p<0.001$). The mean difference between the two groups was 4.3 tests (95% confidence interval (CI) 3.00-5.61). The anticoagulation control was significantly better in WMTAC patients, with 65.1% of them achieving the target INR as compared to 46.0% among UMC patients ($p<0.001$). In relation, the mean percentage TTR was significantly higher in WMTAC patients (66.6% (SD 13.6%) versus 45.5% (SD 21.4%), $p<0.001$). The mean difference was

21.1% (95% CI 12.7-29.6). Similar results were obtained in terms of the percentage of expanded TTR (79.0% (SD 12.9%) versus 55.8% (SD 22.9%), p<0.001). The mean difference was 23.2% (95% CI 14.3-32).

The complications of warfarin therapy were presented in Table 3. There was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. The compliance score showed a significant difference between the two groups with WMTAC patients scored 1.45 (SD 0.97) and UMC patients scored 2.29 (SD 1.23) (p=0.002), indicating that WMTAC patients had better compliance (Table 4). The mean difference between the groups was -0.8 (95% CI -1.4 - -0.3). As shown in Table 5, the follow up default rate was significantly lower in the WMTAC group (3.0%) compared to patients in the UMC group (22.2%) (p=0.038). Ten out of 45 UMC patients defaulted their follow-up appointment at least once during the study period while only one of the 33 WMTAC patients did not attend their appointment once.

Table 2: Anticoagulation control of in WMTAC and UMC patients (n=78)

Variables	WMTAC (n=33)	UMC (n=45)	Statistics (df)	P-value
No. of INR readings, n	395	346	3.24 (1) [a #]	0.072 [a]
INRs test / patient, mean (SD)	12.0 (2.9)	7.7 (3.0)	6.394 (76) [b *]	<0.001 [b]
INRs within range, n (%)	257 (65.1)	159 (46.0)	27.354 (1) [c #]	<0.001 [c]
% TTR, mean (SD)	66.6 (13.6)	45.5 (21.4)	4.986 (76) [b *]	<0.001 [b]
% Expanded TTR, mean (SD)	79.0 (12.9)	55.8 (22.9)	5.216 (76) [b *]	<0.001 [b]
INRs < 1 unit from target, n (%)	0	11 (3.2)	7.482 (1) [c #]	0.006 [c]
INRs > 5, n (%)	5 (1.3)	2 (0.6)	1.522 (1) [c #]	0.217 [c]

[a] Chi-square test; [b] Independent t-test; [c] Chi-square test (Yate's); [#] data presented in X^2-stats (df); * data presented in t-stats (df)
Abbreviation: INR – international normalised ratio; SD – standard deviation

Table 3: Complications of warfarin therapy among WMTAC and UMC patients (n=78)

Variables	WMTAC, n (%)	UMC, n (%)	X^2-stats (df) [a]	P-value [a]
Number of haemorrhage episode			0.993 (2)	0.609
0	30 (90.9)	35 (77.8)		
1	3 (9.1)	8 (17.8)		
2	0	2 (4.4)		
Severity of haemorrhage complications			0.005 (1)	0.943
Minor	3 (9.1)	8 (17.8)		
Major	0	2 (4.4)		
Number of thromboembolic episodes			0.025 (1)	0.874
0	32 (97)	45 (100)		
1	1 (3)	0		

[a] Chi-square test (Yate's)

Table 4: Compliance assessment of WMTAC and UMC patients

Variables	WMTAC	UMC	Statistics (df)	P-value
Compliance score, mean (SD)	1.45 (0.97)	2.29 (1.23)	-3.125 (76) [a *]	0.002 [a]
Compliance Score, n (%)			8.616 (4) [b #]	0.071 [b]
0	5 (15.2)	4 (8.9)		
1	14 (42.4)	8 (17.8)		
2	8 (24.2)	13 (28.9)		
3	6 (18.2)	11 (24.4)		
4	0	9 (20.0)		

[a] Independent t-test; [b] Chi-square test (Yate's); * data presented in t-stats (df); [#] data presented in X^2-stats (df)

Table 5: Default rate of WMTAC and UMC follow up

Clinics	Number of default (%)	X^2-stats (df) [a]	P-value [a]
WMTAC	1 (3.0)	4.313 (1)	0.038
UMC	10 (22.2)		

[a] Chi-square test (Yate's)

Discussion

The results from our study indicated better control of INR values among WMTAC patients as they spent more time in both the TTR and the expanded TTR compared to the UMC group. These differences were statistically significant. There were several studies which compared pharmacist managed anticoagulation services to usual care. The studies that supported our findings include two randomised controlled trials and three observational studies. In one randomized controlled trial conducted in Canada, patients were allocated to either anticoagulation clinics with a pharmacist in three tertiary hospitals (n = 112) or to their family physician practices (n = 109). Patients followed up in the anticoagulation clinics were within the expanded therapeutic range more than patients managed by family physicians (82% vs 76%, $p < 0.05$). High risk INR values (defined as being <1.5 or >5.0) were more often observed in patients managed by family physicians (40% vs 30%, $p < 0.05$) (9). In another study conducted in Hong Kong, patients were randomized to either a pharmacist managed anticoagulation clinic (n = 68) or physician managed service (n = 69). This randomized controlled trial found higher TTR among patients in the pharmacist managed group than the physician managed group (64% vs 59%, $p < 0.001$) (10).

The three observational studies were conducted in Canada, United States and Malaysia respectively. The Canadian research is a prospective cohort study where patients (n = 125) referred to the pharmacist Anticoagulation Management Service (AMS) with at least four months anticoagulation management prior to referral were included in a pre- and post-analysis of anticoagulation control. The anticoagulation control in the AMS improved compared to the standard care before referral (66.5% vs 48.8%, $p <0.0001$) (11). The study conducted by Rudd *et al*. in the United States (n=996) reported significantly improved patients anticoagulation control in pharmacist managed anticoagulation clinics as measured by the TTR (12).

A retrospective cohort study conducted in a tertiary hospital in Malaysia found that WMTAC (n=92) had significantly higher %TTR compared to UMC (n=92) (65.1% vs 48.3%, $p<0.05$). These findings were similar to our study. Moreover, the study also showed that the rate of admission due to warfarin complications and bleeding incidences were reduced in the pharmacist-managed group although it was not significantly different. These findings were similar to our study as there was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. In our study, however, two patients (4.4%) from the UMC group were hospitalised due to hemorrhagic complications of over-warfarinisation. Major haemorrhagic complications were not reported among the warfarin treated patients in the WMTAC group. Three patients (9.1%) from the WMTAC group and eight patients (17.8%) from UMC group were reported to have minor complications such as bruises, gum-bleeding, haematuria, black stool and rectal bleeding.

Compliance assessment is important as warfarin has multiple drug and food interactions and requires frequent laboratory monitoring. Our study used an assessment questionnaire (WCAS) to measure patients' compliance in taking warfarin (8). Our findings showed that WMTAC patients had significantly better compliance towards warfarin therapy compared to UMC patients. This could be attributed to the role of pharmacists in the WMTAC on clinical counselling, patient education, strict INR monitoring, standardized follow-up and comprehensive pharmaceutical care for warfarin treated patients in accordance with protocol (13).

Our study further investigated the default rate among the warfarin treated patients which was not reported by other studies. Findings showed that UMC patients had higher defaulter rate as compared to patients in the WMTAC group. This may be due to the high patient loads and long waiting time in the medical clinics. Hence, WMTAC service can be viewed as a solution to help to share the burden of increasing patient loads. In view of the benefits of WMTAC, such collaborative efforts involving the pharmacists and physicians could be an effective structure for the optimisation of anticoagulation management (14,15). The cooperation between

physicians and pharmacists, not only in anticoagulation management but also in other therapeutic groups, should be considered and expanded to optimise patients' therapeutic outcomes.

There were a few limitations that should be considered. In this study, the WMTAC group was unable to achieve the calculated sample size. Nevertheless, all the WMTAC patients who met inclusion criteria were recruited and post-hoc power analysis revealed more than 80% power. Our study was not powered to detect differences in bleeding or thromboembolic complications between the two groups. Other potential limitation included self-reporting of compliance by the patients. Future research could consider evaluating the effectiveness of WMTAC in a larger cohort and determining the cost effectiveness of WMTAC services.

Conclusion

The pharmacist-managed WMTAC service was able to help patients to achieve better anticoagulation control, higher compliance towards warfarin and lower default rate. These results warrant its effectiveness and continuity in future practice. Therefore, more cooperation between the physicians and pharmacists like the WMTAC services should be promoted to explore the potential to improve patient therapeutic outcomes.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

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