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ORIGINAL ARTICLES

A collaborative care model of anticoagulation therapy in patients with stroke

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Abstract

Background and Objectives: Anticoagulation clinics are widely used for anticoagulation management in many countries, but have only recently began to gain acceptance in Taiwan. Our service model is a physician-managed outpatient clinic collaborating with clinical pharmacist and nurse. This study aimed to evaluate the adequacy of anticoagulation and rates of warfarin-related complications before and after referral to our collaborative anticoagulation clinic (CAC). *Methods:* Stroke patients taking warfarin from the neurology department were identified and referred to the CAC during the 12-month period from February 2009 to January 2010. Quality markers include percentage of international normalized ratio (INR) values in the therapeutic range, frequency of INR monitoring, and frequency of follow-up visits and the mean interval of next INR monitoring after non-therapeutic INRs were compared one year before and after management in the CAC. Using studied patients as self-control, they were included in the analysis if patients had at least 3 months follow-up or 3 INR values both before and after referral. *Results:* A total of 44 stroke patients were included: mean age of 75.0 ± 9.7 years, with a $CHADS_2$ score of 3.71 ± 0.69. The adequacy of anticoagulation was significantly greater during CAC care compared with the period before referral; the percentage of INR within expanded therapeutic range was 60.9% versus 53.7%, respectively (p=0.049). Reduction in sub-therapeutic INR values from 31.8% to 24.2% (p=0.023) contributed mostly to the improved quality of care. The time interval of next INR monitoring after non-therapeutic INRs ($\geq$ 4.0 or $\leq$ 1.5) was also significantly shorter. However, there was no significant difference in the rates of thromboembolic and hemorrhagic events which may be attributed to a small sample size.
Conclusion: Based on results of our study, a CAC may be the optimal structure for anticoagulation management service in the future.

INTRODUCTION

Warfarin has been the mainstay of anticoagulation therapy for several decades. The risk of hemorrhage or thrombosis remains a major concern for healthcare providers if therapy is not maintained within the narrow therapeutic index. Thus, the management of warfarin therapy is extremely challenging in clinical practice.

Numerous studies from Western countries have reported that anticoagulation clinics improved the quality of care in patients receiving warfarin therapy, and reduced the rates of hospitalizations and emergency department visits due to adverse events related to anticoagulation therapy. [1-4] As such, the American College of Chest Physicians recommends the use of specialized anticoagulation clinics to improve the quality and safety of anticoagulation therapy. [5]

In Taiwan, anticoagulation therapy was prescribed and monitored solely by physicians during clinic visits. Physicians not only address anticoagulation management but also all of the patient's other medical problems (traditional care setting). Despite known benefits and the strong recommendations, anticoagulation clinic has yet to be implemented in Taiwan.

To address this knowledge gap, we performed a retrospective cohort study comparing the model of physician-managed anticoagulation therapy with a collaborative clinic using physicians, nurses, and clinical pharmacists by measuring international normalized ratios (INRs), thromboembolic events, and bleeding complications. We hypothesized that the collaborative clinic would have a higher percentage of INRs in therapeutic range, more frequent follow-up visits and INR monitoring

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after sub- or supra-therapeutic INRs than the traditional care setting.

METHODS

A collaborative anticoagulation clinic (CAC) using physician, clinical pharmacist, and nurse was initiated in February 2009 as a pilot project at the Mackay Memorial Hospital, Taipei, Taiwan.

Roles of the physician, pharmacist and nurse

The physician was responsible for developing the care plan, including interpretation of INR results, determination of warfarin dose adjustments, and timing of follow-up visits and frequency of INR monitoring. Regarding the frequency of follow-up visits, patients with stable INR values were seen in the anticoagulation clinic once every 4 to 8 weeks, whereas those with fluctuating INR values were seen more frequently at a two weeks interval. Generally, INR was monitored one week after warfarin dose adjustment. Otherwise, the frequency of INR monitoring was once every 4 to 8 weeks. During periods of INR fluctuations, physician decides the date of the next visit or the next INR test date with or without clinic visit.

Working collaboratively with the physician, the clinical pharmacist provided a one-on-one educational session to the patients. During this session, the patient is informed of the indication of warfarin therapy, bleeding and thrombotic complications, the need for compliance with therapy and the importance of INR monitoring. Further, factors that may affect warfarin therapy (e.g., medications, food, and lifestyle habits) are explained. A written instruction for warfarin dosing and educational handouts was also provided. The reasons for fluctuations of the INR were documented by the clinical pharmacist during each visit if patient had non-therapeutic INR values. Subsequently, for each follow-up visit, patients are also seen in one-to-one session for education to be reinforced.

During each patient encounter, the clinical pharmacist documents findings in a custom-made computer program using Microsoft® Access 2003. This computer program was designed to (1) store patient's demographic information; (2) record warfarin doses and INR values; (3) evaluate the quality of INR control. Three tabs could be found on the main screen of the program. Each of those was "Basic Information", "Past Medical History" and "Follow-Up and Assessment", designed to access different patient information. Statistical function could be performed to help understand demographics of our population and quality of INR control. With the assistance of computer program, clinical pharmacists could become familiar with the patient quickly and organize patient data electronically.

The nurse worked as a reminding system by prompt reporting of central laboratory results to the physician after each INR drawn. If there is any change in the warfarin dosing instructions, the nurse was solely responsible for contacting the patients by telephone and delivering the instructions of the physician. Patients who missed their appointments or INR monitoring were also contacted by the nurse to ascertain the reason, to provide adherence counseling, and to reschedule the visit or INR test date.

Patients

Stroke patients receiving warfarin were referred to the CAC during the 12-month period from February 2009 to January 2010. Referrals were made at the discretion of the prescribing physician. Major reasons for referrals to the CAC included frequent INR fluctuations, non-adherence, as well as multiple risk factors for recurrent stroke, such as cardiovascular diseases, atrial fibrillation (AF), and cerebral artery stenosis.

Using studied subjects as self-control, a retrospective chart review was conducted to collect data dated one year before and after referral. Patients were included in the analysis if they had at least 3-month follow-up or 3 INR values both before and after referral. Patients were excluded if they did not meet these criteria. This study protocol was approved by the Institutional Review Board of Mackay Memorial Hospital. Because of the nature of the study, the requirement for informed consent was waived.

Outcome measures

The primary study outcome was the percentage of INR values in the therapeutic range. This was determined by calculating the number of INR values within range divided by the total number of INR values.[6] For patients with ischemic stroke or transient ischemic attack (TIA) and AF, the recommended therapeutic INR range was 2-3.[7] An expanded therapeutic INR range, defined as therapeutic range ± 0.2, was used in our study since minor fluctuations within this range was considered clinically insignificant without need for dose adjustment. Thus, the expanded therapeutic INR range for aforementioned patient population was 1.8-3.2.

The secondary study outcomes were frequency of follow-up visits and INR monitoring, and the mean interval of next INR monitoring following non-therapeutic INR (⩾4.0 or ⩽1.5). Bleeding and thromboembolic events during warfarin treatment were documented as safety indicators. Etiologies for non-therapeutic INRs were also analyzed.

Statistical analysis

All of the analysis was performed with SPSS 12.0 for Windows. Continuous variables were presented as mean ± standard deviation (SD). Chi-squared test was used for nominal data to analyze differences in percent of INR in range. Data before and after referral were compared using the student's paired t-test for continuous data such as frequency of follow-up visit and INR monitoring. Unpaired t-test was used for continuous data to detect differences in time interval to the next INR monitoring. A p value of <0.05 was considered statistical significant.

RESULTS

Patient demographics

From February 2009 to January 2010, a total of 69 patients were referred to the CAC. Of these, 25 patients were excluded from analysis as they had less than 3 months follow-up or less than 3 INR values either before or after referral. The remaining 44 patients were included in the analysis. The demographic characteristics of the patients are listed in Table 1. All patients had a past history of stroke, including ischemic stroke (n=42), TIA (n=4) and hemorrhagic stroke (n=1). Of these, two patients had both ischemic stroke and TIA and one patient had both ischemic and hemorrhagic stroke. Prior to referral to the CAC, one patient who used warfarin for secondary stroke prevention suffered from hemorrhagic stroke and another two had recurrent ischemic stroke.

The most common indications for warfarin therapy were AF (86.4%), rheumatic mitral valve (6.8%), cerebral artery stenosis (4.6%) and prosthetic heart valve (2.3%). The average $CHADS_2$ score was 3.71 ± 0.69 for patients with chronic or paroxysmal AF, indicating a high-risk population for stroke. The prevalence of treatable vascular risk factors of hypertension, diabetes and dyslipidemia were 84.1%, 20.6% and 65.9%, respectively. All patients had more than two risk factors for stroke. Details of patient risk factors and co-morbid diseases are shown in Table 2.

Quality of anticoagulation therapy

Table 3 summarizes the adequacy of anticoagulation before and after referral. The mean number of days on warfarin therapy and the mean interval between clinic visits were not statistically different between the two periods. Patients after referral to the CAC had more INR measurements than prior management. Before referral, 7.1 ± 2.5 INR measurements were performed compared with 9.7

Table 1: Patient characteristics

Characteristics	N=44
Male (%)	22 (50)
Age (mean ± SD)	75.0 ± 9.7
Atrial fibrillation (%)	38 (86.4)
$CHADS_2$ score (mean ± SD)	3.71 ± 0.69
Stroke risk factors (%)	
Age ⩾75 years	21 (47.7)
Prior stroke or TIA	44 (100)
Hypertension	37 (84.1)
Diabetes mellitus	9 (20.5)
Congestive heart failure	7 (15.9)

Table 2: Patient co-morbid diseases

Patient risk factors	n (%) of patients
Ischemic stroke	42 (95.5)
TIA	4 (9.1)
Hemorrhagic stroke	1 (2.3)
Hypertension	37 (84.1)
Coronary artery disease	5 (11.4)
Myocardial infarction	3 (6.8)
Ischemic heart disease	11 (25.0)
Chronic AF	22 (50.0)
Paroxysmal AF	16 (36.4)
Cardiomyopathy	1 (2.3)
Rheumatic heart disease	3 (6.8)
Chronic heart failure	7 (15.9)
Chronic kidney disease	9 (20.5)
Diabetes mellitus	9 (20.5)
Hyperlipidemia	29 (65.9)
Hyperthyroidism	3 (6.8)

± 4.2 INR measurements after referral (p=0.001). In addition, patients had their INR checked on average every 21.9 ± 6. 6 days in the CAC vs. every 34.8 ± 16.2 days during traditional care setting (p<0.0001).

Distributions of INR categories before and after referral are shown in Figure 1. Using the expanded range, a significant increase in anticoagulation control from 53.7% prior to referral to 60.9% during the CAC care (p=0.049). Patients had significantly more frequent sub-therapeutic INR values during traditional care as compared with the period after referral (31.8% vs. 24.2%, p=0.023). The percentage of INR values above range did not differ before and after referral (14.5% vs. 14.8%, p=0.893). Patients with both sub- or supra-therapeutic INR values received quicker follow-up INR testing during the CAC care.

The incidence of bleeding and thromboembolic events is presented in Table 5. No difference in bleeding events was noted between the two periods (10 vs. 12, p=0.670). However, there were more documented minor bleeding events during the CAC care.

Among the 117 INR measurements during the follow-up visits in the CAC, etiologies for non-therapeutic INR values were analyzed (Table 4). The most prevalent causes included no clear explanation (57.3%), change in dietary vitamin K (12.8%), and change in concomitant medications (10.3%).

DISCUSSION

To the best of our knowledge, our study was the first one to describe a physician-managed anticoagulation service, collaborating with clinical pharmacist and nurse in an attempt to improve the quality of anticoagulation therapy. We demonstrated significant improvement in anticoagulation care for patients during CAC care compare with their prior management. We found better control of INR values when warfarin

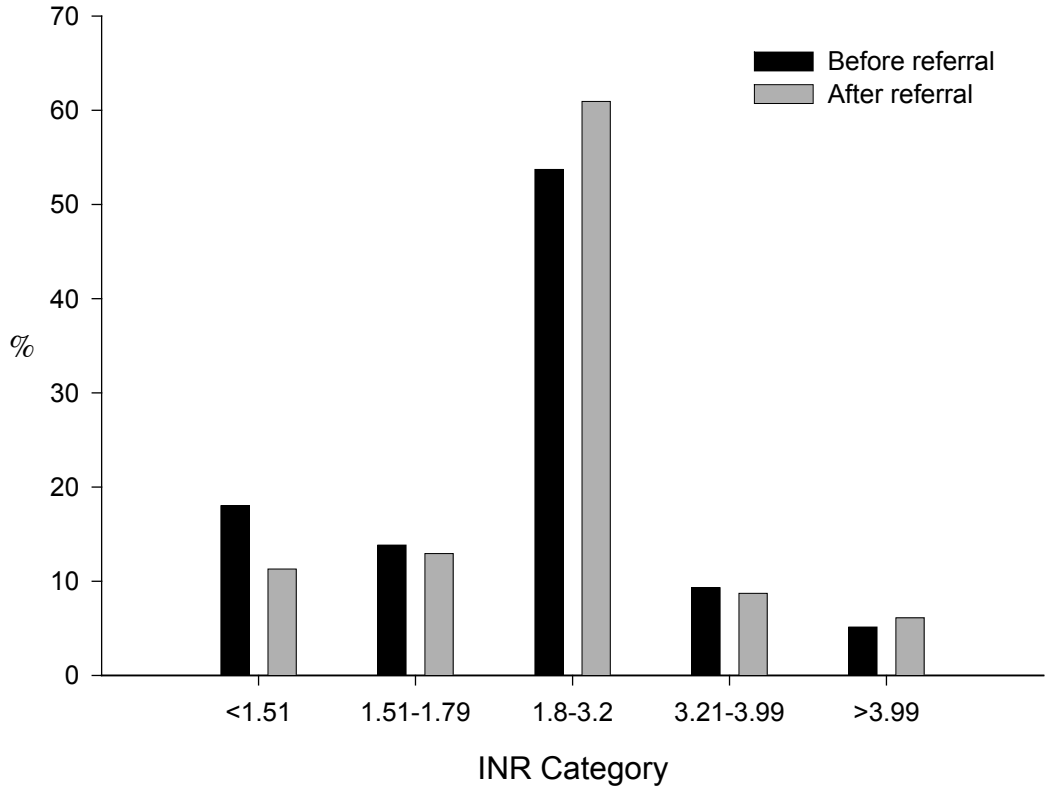

Figure 1: Distributions of INR categories before and after referral

management was performed by a CAC than by a physician in the traditional care setting. This was reflected by an increase in the percentage of INR values in the expanded therapeutic range from 53.7% to 60.9% (p=0.049). Similar to other studies, we used expanded therapeutic INR range[8,9] to evaluate the adequacy of anticoagulation since fluctuations within ± 0.2 was considered clinically insignificant without need for dose adjustments. However, the optimal anticoagulation intensity for Chinese patients has not been examined in randomized clinical trials. Results from a retrospective cohort study of Hong Kong Chinese patients receiving warfarin for indications with target INR of 2-3 found that an INR of 1.8-2.4 was associated with the lowest incidence rate of major bleeding or thromboembolic events.[10] Furthermore, results from four available studies also showed that INRs of 1.6-1.9 provide 80-90% of the protection against stroke in patients with AF.[11-14] Thus, the lower range of therapeutic INR might be targeted to 1.8 for our stroke patients with AF. On the other hand, patients with an INR of 3.2, which is the upper range of the expanded therapeutic INR, would require careful monitoring of bleeding complications since the Hong Kong study found bleeding events increased from 4 to 11.7 events per 100 patient-years as INR increased from 2.4 to 2.9.[10]

Sub-therapeutic INR value had important consequences: there was an approximately 16-fold increase in the rate of thromboembolism during period of low INR.[15] In our study, reduction in sub-therapeutic INR values contributed mostly to the improved quality of care. A significant decrease in percent of INR below therapeutic range (31.8% vs. 24.2%) was noted on transition to CAC care. Our results are in concordance with the finding that sub-therapeutic INR is significantly higher in the traditionally monitored patients.[16] A likely explanation is the patients in the CAC care received quicker follow-up visit or telephone contact for adjustment of their warfarin dose. On the other hand, we found no significant difference in supra-therapeutic INR values both before and after transition to CAC care. However, after transition, minor bleeding events did occur more frequently because physician seems to be more proactive in trying to achieve therapeutic INR values by faster adjustment of warfarin dosage.

Table 3: Comparison of anticoagulation control before and after referral

Variables	Before	After	*P*-value
	Mean ± SD		
Number of days on warfarin therapy	243.4 ± 113.2	211.6 ± 98.7	0.155
Number of clinic visits per patient	6.5 ± 2.2	6.2 ± 2.9	0.521
Interval between clinic visits (days)	36.9 ± 16.6	34.4 ± 10.9	0.325
INR measurements per patient	7.1 ± 2.5	9.7 ± 4.2	0.001
Interval between INR measurements (days)	34.8 ± 16.2	21.9 ± 6.6	<0.001
Mean interval to next INR after sub-therapeutic INR ⩽ 1.5 (days)	21.6 ± 13.7	15.9 ± 8.3	0.021
Mean interval to next INR after supra-therapeutic INR ⩾ 4 (days)	16.7 ± 15.5	8.6 ± 8.2	0.043
Therapeutic INR control* (%)			
Percent of INR in range	53.7	60.9	0.049
Percent of INR above range	14.5	14.8	0.893
Percent of INR below range	31.8	24.2	0.023

* Expanded therapeutic INR range = therapeutic INR range ± 0.2

We found significant improvement in the mean interval to recheck an INR following INR values of ≤1.5 and ≥4. The time to response after supra-therapeutic and sub-therapeutic INR values in our study was shorter in the CAC care (8.6 and 15.9 days), but much longer (16.7 and 21.6 days) in the traditional care setting. This is in line with many observational studies which reported that the time between non-therapeutic INR values and follow-up INR testing was significantly shorter in the anticoagulation management service.[3,16]

Although the mean number of days on warfarin therapy was not statistically significant between the two periods, the mean number of INR measurements per patient was significantly higher after the CAC care. These results show a

Table 4: Etiologies for non-therapeutic INRs

Explanations	n (%)
Initiation of therapy	3 (2.6)
Response to previous change in warfarin dose	10 (8.6)
Warfarin held intentionally	7 (5.9)
Non-adherence or incorrect use	3 (2.6)
No clear explanation	67 (57.3)
Change in dietary vitamin K	15 (12.8)
Change in prescription, nonprescription or herbal medications	12 (10.3)

Table 5: Warfarin related adverse events

Adverse events	Before	After	*P*-value
Bleeding events	10	12	0.670
Bruising	2	1	0.564
Gum bleed	2	5	0.257
Conjunctiva bleed	1	0	NA
Hematuria	1	1	1.000
Tarry stool	3	3	1.000
Hemoptysis	0	2	NA
Intracerebral haemorrhage	1	0	NA
Ischemic stroke	2	0	NA

NA = not applicable

tendency towards adequate INR monitoring in the CAC setting. Despite the best efforts of the CAC, we found no significant differences in the rates of warfarin-related adverse events before and during CAC care. The most potential reason for this is the relatively small sample size. Another possible explanation is the failure of the physician in the traditional monitoring to specifically asked patients about minor bleeding events unless mentioned by the patients. Even when mentioned, the event might not be documented by the physician because no intervention is required.

Although not the focus of our study, we also try to identify the causes of non-therapeutic INR values. The most prevalent etiologies included change in dietary vitamin K intake, interaction with prescription and non-prescription drugs, interaction with dietary supplements or herbal remedies, response to change in dosage, initiation of therapy, and non-compliance or dosing error. Interestingly, in contrast to other study[17], the results of our study show a considerably high rate (57%) of no clear explanation for non-therapeutic INRs despite the best efforts of our clinical pharmacist.

Our study has several limitations. First, we used a before-and-after study design for evaluation. As randomization was not feasible, the analysis was nonrandomized and retrospective in nature. Second, this study was conducted in a single anticoagulation clinic and the data were limited by the relatively small sample size which may not be completely generalizable. Third, the absence of a standardized template for documentation in the traditional care setting might have underestimated the incidence of warfarin-related adverse events. In addition, the patients in this study were followed by a dedicated anticoagulation clinic; which increase the quality of care after transition from traditional monitoring to a specialized anticoagulation clinic. Finally, the small number of bleeds made impossible to identify the predictors of major bleeding events. Nevertheless, it is reasonable to assume that our data are reflective of the current clinical practice in Taiwan.

In conclusion, our data demonstrated that a specialized clinic specifically devoted to the management of anticoagulation therapy achieved significantly better INR control compared with the traditional setting. A collaborative care model may be superior to other anticoagulation management service models in providing adequate anticoagulation to the patients; its results should be verified in future prospective studies.

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