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Original Article

Effects of Ambulatory Clinical Pharmacy Anticoagulation Service on the Outcomes of Anticoagulation Knowledge

Chien-Ying Lee[1,2], Ya-fang Tsai[3], Kuang-Hua Huang[4], Yu-Hsiang Kuan[1,2*]

[1] *Department of Pharmacology, Chung Shan Medical University*
[2] *Department of Pharmacy, Chung Shan Medical University Hospital*
[3] *Department of Health Policy and Management, Chung Shan Medical University*
[4] *Department of Health Service Administration, College of Public Health, China Medical University*

Objective: The objective of this study was to assess patient knowledge of anticoagulation improvement using a patient education sheet or booklet about warfarin provided by clinical pharmacy anticoagulation service (CPAS). We investigated whether the material was helpful to these patients, whether it improved prothrombin time (PT)/ international normalized ratio (INR) monitoring status, and whether it reduced emergency department (ED) visits and hospital admissions for hemorrhage and thromboembolism.
Materials and Methods: We included patients aged 18 years old and above who could communicate in Mandarin Chinese or Taiwanese with a pharmacist, who were willing to receive warfarin education, and willing to participate in this study. Patients received tests before and after receiving warfarin patient education. To evaluate patient's attitude and opinion, we administered questionnaires after they completed the education program. We also investigated INR monitoring status, ED visits, and hospital admissions for hemorrhage and thromboembolism events during the 6 months prior to before the education program and also followed-up for 6 months after completing the CPAS program.
Results: After CPAS, average scores were found to have significantly increased ($p<0.001$). Days within INR target improved significantly and days below INR target and days above INR target decreased significantly ($p<0.001$). The number of hemorrhage and thromboembolism events requiring ED visits and hospital admissions decreased significantly ($p<0.001$).
Conclusion: Clinical pharmacy services in the ambulatory clinic systems of this health system had a positive effect on outcomes. After pharmacist-directed CPAS program, average outcome scores were increased significantly with regard to usage of warfarin and similar medications. Patients achieved their target INR ranges significantly more often after CPAS care and had fewer ED visits and hospitalizations due to thromboembolism and hemorrhage events.

Key words: Warfarin, Patient education, Prothrombin time (PT), International normalized ratio (INR)

* Corresponding Author: Yu-Hsiang Kuan
Address: #110, Section 1, Jian-Guo North Road, 40242, Taichung, Taiwan
Tel: 886-4-24739595 ext. 11664
Email:kuanyh@csmu.edu.tw

Introduction

Prothrombin time (PT), also known as PT/ INR, and its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) are measures of the extrinsic pathway of coagulation. These measures are used to determine the clotting tendency of blood when determining

warfarin dosage. PT is used in conjunction with the activated partial thromboplastin time (aPTT), which measures the intrinsic pathway. The reference range for prothrombin time depends on the analytical method used, but usually ranges around 12-13 seconds, and the INR in absence of anticoagulation therapy is 0.8-1.2. For most patients, an INR between 2 and 3 is therapeutic. In some cases, if more intense anticoagulation is thought to be required, the target range may be as high as 2.5 to 3.5 depending on the indication[1,2].

Anticoagulants are extensively utilized to treat and prevent recurrent thromboembolic disorders[3]. Oral vitamin K antagonists, such as warfarin, are among the most commonly prescribed and potentially dangerous class of medications[4]. INR is typically used to monitor patients on warfarin or related oral anticoagulant therapy. Maintaining a patient within a therapeutic INR is the main aim of treatment with warfarin. Maintaining INR within the prescribed range is essential to preventing complications, including bleeding when INR is too high and thromboembolism when it is too low. Multiple factors, including diet, alcohol, concurrent medication use, illness, and adherence, can adversely affect the safety and efficacy of warfarin[5]. For many high-risk drugs, such as warfarin, there is a positive correlation between patients' warfarin knowledge and the number of INR values within the target range[6].

Prioritizing the educational domains, standardizing the educational content, and delivering the content more efficiently is necessary to improve the quality of anticoagulation with warfarin[7]. It is essential that patients receiving anticoagulation medication be adequately counseled. Therefore, it is critical that the information they receive be both accurate and understandable.

The clinical impact of pharmacist-managed clinical anticoagulation service has been well documented. Due to the high frequency self-usage of traditional Chinese medicines in Taiwan, patients require more intensive education when they receive oral anticoagulation therapy. The objective of this study was to assess improvement in patient knowledge of anticoagulation therapy using patient education sheets or booklets about warfarin provided by pharmacists to find out whether these materials and education program are helpful. We investigated INR monitoring status, emergency department visits and hospital admissions for hemorrhage and thromboembolism events in patients six months before they received these educational materials and also followed up these patients for 6 months after they completed the clinical pharmacy anticoagulation service (CPAS) materials.

Materials and Methods

Subjects

When ambulatory pharmacists received warfarin prescriptions, they were actively asked to enter the drug information (DI) room for CPAS. If they were willing to receive warfarin patient education, they were included in our study. We included outpatients receiving warfarin and diagnosed as having one of the following indications: stroke, atrial fibrillation, valvular heart disease, prosthetic cardiac valves, deep vein thrombosis, pulmonary embolism.

Inclusion Criteria

Patients were included in the study if they were at least 18 years of age, had received at least one prescription for warfarin, had at least two INR values measured during the 6-month evaluation period, and were able to communicate in Chinese or Taiwanese with a pharmacist.

Exclusion Criteria

Patients were also excluded of they refused to receive warfarin patient education or if they had difficulty communicating with the pharmacists. Patients receiving warfarin for the prevention of venous thromboembolism following a high-risk surgical procedure (e.g., hip or knee replacement surgery) were also excluded because the duration of warfarin therapy following high-risk surgery is often only days to weeks.

Investigation Method

The patients were administered a one hundred-point anticoagulation education test: 30 points for relationship between warfarin and disease, 17

points for interaction of warfarin and food and herbals, 6 points for interaction between warfarin and drugs, 17 points for the relationship between warfarin and INR and 30 for danger signs.

In order to follow-up these patients, we continued keeping each patient's records and maintaining data integrity. Before each patient received warfarin, he or she was administered the test tso that the pharmacist could determine what the patient knew about warfarin. After education, each patient also received a warfarin education booklet to use as reference. After the program, the patients were administerd the knowledge evaluation test one more time to determine what they had learned and now understood about warfarin usage.

To evaluate patient's attitudes toward the education program, we administered questionnaires to the patients when they completed the program. An expert was consulted to evaluate the reliability and validity of questionnaire content.

The hospital reference laboratory PT is 8-12 seconds. INR value is calculated based on PT automatically as a reference for clinicians. We collected each patient's INR monitoring status, emergency department (ED) visits and hospital admissions due to hemorrhage and thromboembolicsm events 6 months before the education program began and 6 months after completing the CPAS program. We used a method developed by Rosendaal and colleagues to assess adequacy of anticoagulation by measuring the proportion of time patients spent within their indicated INR range (target INR ± 0.5 units)[8]. We collected hospital utilization data by coding all instances of ED visits and hospital admissions the International Classification of Diseases (ICD-9). These ICD codes were classified as hemorrhagic or thromboembolic.

Statistical methods

Student's test was used to test numerical data, and chi-square test for categorical data. All statistical operations were performed using the SPSS 10.0 software package. A p-value of less than 0.05 was considered significant.

Results

In total, we enrolled 61 patients (26 men, 25 women) with a mean age of 66 years old. The most common disease was valvular heart disease (n=19, 37.2%), the second was atrial fibrillation (n=14, 27.4%), and the third was deep vein thrombosis (n=9, 17.6%). (Table 1)

The evaluation test after CPAS revealed significant increases in total score. Overall it was found to have improved by 30.43 ± 5.53 points ($p<0.001$), especially in those 50-59 years old. The

Table 1. Baseline characteristics of the patients

Characteristics	Male	Female	Total
Gender (n, %)	26 (50.98)	25 (49.02)	51
Age (Mean ± SD years)	65.81 ± 11.33	66.64 ± 11.94	66.22 ± 11.52
Age group (n)			
40-49	1	2	3
50-59	7	5	12
60-69	8	4	12
70-79	7	10	17
80-89	3	4	7
Indications (n)			
Stroke	1	3	4 (7.8%)
Atrial fibrillation	4	10	14 (27.4%)
Valvular heart disease	12	7	19 (37.2%)
Deep vein thrombosis	6	3	9 (17.6%)
Pulmonary embolism	0	1	1 (2%)
Myocardial infarction	2	1	3 (6%)
Prosthetic cardiac valves	1	0	1 (2%)

Table 2. Distribution of average points and age

Persons	Average points before education	Average points after education	Increased average points	p value
51	22.45 ± 9.37	52.88 ± 11.68	30.43 ± 5.53	<0.001
Age(n)				
40-49 (3)	22.67 ± 0.58	55.67 ± 1.53	33.00 ± 2.00	<0.001
50-59 (12)	23.25 ± 8.83	54.83 ± 11.78	31.58 ± 5.58	<0.001
60-69 (12)	27.58 ± 8.63	58.25 ± 10.22	30.67 ± 4.72	<0.001
70-79 (17)	18.18 ± 10.13	48.71 ± 13.49	30.53 ± 6.29	<0.001
80-89 (7)	22.57 ± 8.54	49.29 ± 8.58	26.71 ± 5.25	<0.001

improvement of average scores was less in patients 80-89 years old, compared patients of other age groups. (Table 2)

The average scores for the outcome of patient education were increased significantly in warfarin and variant drugs ($p<0.001$). The increase in average points indicating a knowledge of the relationship between warfarin and disease was 8.98 ± 2.73, the interaction between warfarin and food–herbs 5.51 ± 1.83, the interaction between warfarin and drugs 1.76 ± 0.95, the relationship between warfarin and INR 5.31 ± 1.89 and the danger signs 8.86 ± 2.53. (Table 3)

The result the questionnaire for patient's attitude toward the information sheet and booklet were 47% and 53%, respectively, after instruction by the pharmacist. This study revealed that warfarin education should be divided into two stages (70.6%) rather than one stage (29.4%) ($p<0.001$). Two-stage warfarin education was found to better improve patient knowledge of warfarin usage. Most of these patients expressed a willingness to participate this kind of patient education activity again (82.4%) ($p<0.001$). (Table 4)

After CPAS, days within INR target improved significantly from 40.3 % to 62.5 % ($p<0.001$), days below INR target and days above INR target decreased significantly ($p<0.001$). (Table 5)

Table 3. Distribution of average points of warfarin and varients

	Total points	Average points before education	Average points after education	Increased average points	p value
Relationship between warfarin and disease (1-6)	30	8.35 ± 4.00	17.33 ± 4.28	8.98 ± 2.73	<0.001
Interaction of warfarin and food -herbal (7-11)	17	3.51 ± 2.17	9.02 ± 2.61	5.51 ± 1.83	<0.001
Interaction between warfarin and drug (12)	6	2.12 ± 1.29	3.88 ± 1.01	1.76 ± 0.95	<0.001
Relationship between warfarin and INR (13-17)	17	3.04 ± 2.58	8.35 ± 3.35	5.31 ± 1.89	<0.001
Danger signs (18-20)	30	5.43 ± 2.94	14.29 ± 3.63	8.86 ± 2.53	<0.001

Table 4. The result of patient's attitude and opinion questionnaire

Patient education form		
Patient education sheet	Patient education booklet	p value
24 (47%)	27 (53%)	>0.05
The stage of warfarin education		
one stage	two stage	p value
15 (29.4%)	36 (70.6%)	<0.001
Willingness to participate this kind of patient education again		
No	Yes	p value
9 (17.6%)	42 (82.4%)	<0.001

Table 5. INR monitoring outcomes

Therapeutic INR control (%)	Before CPAS	After CPAS	p value
Days below INR target	32.4	20.1	<0.001
Days within INR target	40.3	62.5	<0.001
Days above INR target	27.3	17.4	<0.001

INR, international normalized ratio; AMS, anticoagulantion management service.

After CPAS, the number of ED visits and hospital admissions due to hemorrhagic events decreased significantly ($p<0.001$) and the number of ED visits and hospital admission due to thromboembolic events also decreased significantly ($p<0.001$). (Table 6).

Discussion

We demonstrated substantial improvement in anticoagulant care for patients after CPAS compared to their prior management. After pharmacist-directed CPAS program, the average outcome scores for patient education increased significantly with regard to their knowledge about usage of warfarin and its variants. Patients reached their desired INR ranges significantly more often during CPAS care and had fewer ED visits and hospital admissions due to thromboembolic and hemorrhagic events.

Environmental factors such as drugs, diet, and various disease states can alter the pharmacokinetics of warfarin. Several disease states may affect warfarin metabolism, including thyroid disease, liver disease, renal disease, febrile illness, cancer and congestive heart failure. Therefore, it is necessary to carefully monitor anticoagulant therapy in patients with diseases that have the potential to affect warfarin response and affect its safety and efficacy[9]. Warfarin is a racemic mixture with the (S) form being five times more potent than the (R) form[10]. St. John's wort and some ginseng formulations may potentially diminish warfarin's anticoagulation effect[11]. Foods may affect warfarin levels particularly if they contain high vitamin K content[11]. The interaction between warfarin and other drugs as well as herbal medicines and food is complicated. However, the increase in warfarin and drug score was not significant. We would expect a greater change, but this might have been confounded by the frequent use of traditional Chinese medicine in Taiwan. Patients receiving warfarin in Taiwan may require more intensive education. Most of the patients in our study preferred this two-stage warfarin education program and expressed a willingness to participate in this kind of patient education program again, suggesting that pharmacist-directed anticoagulation education is useful for these patients. One previous study has suggested that enhanced patient education may lead to superior patient knowledge regarding warfarin and may subsequently improve long-term patient safety associated with anticoagulation therapy[12].

Use of an existing healthcare handbook overcame several systemic barriers by facilitating warfarin patient education. While the intervention was associated with better short-term warfarin knowledge, follow-up may be required to optimize its benefits. Patients also need to be reminded of certain pieces of important information, including INR target range and danger signs. We provided

Table 6. ED visits and hospital admissions before and after CPAS

Events	Before CPAS	After CPAS	p value
Hemorragic, ED	42	8	<0.001
Hemorragic, hospital	22	9	<0.05
Thromboembolic, ED	21	7	<0.05
Thromboembolic, hospital	48	6	<0.001

ED, emergency department; AMS, anticoagulantion management service.

a warfarin booklet in this study because the interactions between warfarin and other drugs is complicated for our patients.

The average scores for the outcome of patient education were increased significantly in warfarin and its variants, including the relationship between warfarin and disease, the interaction of warfarin and food and herbs, the interaction between warfarin and drugs, the relationship between warfarin and INR and danger signs. Our results showed that the improvement of average scores was less for patients between 80 and 89 years old, suggesting several gaps in knowledge about medicine in the elderly. This highlights the importance of pharmacist-centered anticoagulation education. Our result is similar to one study that indicated access to counseling resulted in significantly improved warfarin knowledge scores and that reported an association between improved knowledge better compliance and control[13].

The therapeutic range for anticoagulants is narrow: an INR of less than 2 increases the risk of thromboembolism, and an INR of more than 4.5 increases the risk of major bleeding[14]. The main goal of this program was to teach patients practical skills that would lead to accurate INR results. It is important for patients receiving warfarin to maintain an INR within the target range. In this study, we found significantly improved score in their knowledge regarding the use of warfarin and their INR values. Other studies have also reported a positive correlation between patients' knowledge of warfarin and number of INR values within goal range[6] and better anticoagulation control[15]. To assess whether any apparent benefits of the anticoagulation clinic were mediated by differences in therapeutic INR control, we included the percentage of time spent within the target INR range as a covariate in the model. The results of this study are supported by other studies[16-19] reporting that clinically trained pharmacists using a structured, specialized approach to managing oral anticoagulation therapy can achieve superior outcomes. We found adequacy of anticoagulant control expressed as days within INR target after CPAS education. After CPAS, the days within INR target increased and day below INR target and days above INR targets decreased significantly.

In addition, after CPAS, the number of ED visits and hospital admissions due to hemorrhagic and thromboembolic events decreased significantly, suggesting that CPAS had great impact on reducing thromboembolic and hemorrhagic complications. These results are similar to those reported by others[20,21]. Widespread implementation of warfarin education by pharmacists may contribute significantly to improved warfarin therapeutic outcomes[22].

Study limitations

This study has some limitations. First, we used a before/after design for evaluation, as randomization was not feasible given the complicated nature of the cases referred to our specialty service. Second, our data are limited by the relatively small sample size due to the fact that we used strict inclusion criteria to comprehensively evaluate INR control and associated outcomes. Another limitation was that the initial identification of potential anticoagulation therapy adverse events depended upon the availability of electronic claims and referral datasets.

Conclusion

The effect of clinical pharmacy services in the ambulatory clinic systems of this health system has been dramatic. After participating in this pharmacist-directed CPAS program, the patient's average scores regarding knowledge of usage of warfarin and its variants increased significantly. Patients remained within their desired INR range significantly more often and experienced fewer thromboembolic and hemorrhagic events after CPAS care.

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Original Article

執行門診臨床藥學服務對抗凝血藥物認知之提升及成效評估

李建瑩[1,2] 蔡雅芳[3] 黃光華[4] 關宇翔[1,2*]

[1] 中山醫學大學 藥理科
[2] 中山醫學大學附設醫院 藥劑科
[3] 中山醫學大學 醫療產業科技管理學系
[4] 中國醫藥大學 醫務管理學系暨碩士班

目的：評估門診藥師執行臨床藥事服務的成效，利用warfarin衛教單張或手冊教導使用warfarin患者後評估患者對抗凝血知識認知提升的情形，同時評估患者凝血酶原時間/國際標準凝血酶原時間比值變化之情形、血栓或出血而急診和住院的情形是否有改善。

材料與方法：收納條件為可以中文或台語與藥師溝通之18歲以上且願意接受warfarin衛教的門診患者，經由藥師利用warfarin衛教單張或手冊衛教，患者在接受衛教前後受接受測驗，評估衛教執行成效，同時利用問卷調查來了解接受衛教患者的態度與意見，也了解患者接受衛教前6個月及接受衛教後6個月的INR值改變情形、血栓或出血而急診和住院的情形。

結果：經由藥師臨床藥事服務，患者接受warfarin衛教後的平均分數明顯提升（$p<0.001$），患者的INR值在目標值的期間顯明增加（$p<0.001$），因血栓或出血而急診和住院的情形大幅減少（$p<0.001$）。

結論：此研究結果顯示經由藥師介入的門診臨床藥事服務，warfarin衛教成效顯著，患者接受warfarin衛教後的分數明顯增加，患者INR值在目標值的期間顯明增加，因血栓或出血而急診和住院的情形大幅減少。

關鍵詞：Warfarin、病患衛教、凝血酶原時間、國際標準凝血酶原時間比值

* 通訊作者：關宇翔
通訊地址：40201台中市南區建國北路一段110號
聯絡電話：04-24739595分機11664
電子信箱：kuanyh@csmu.edu.tw