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THE EFFECTS OF PHARMACIST'S COUNSELING ON WARFARIN-RELATED CLINICAL OUTCOMES IN PHARMACY'S AMBULATORY CARE

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Abstract: The objective of this study was to determine the effects of the pharmacist counseling on warfarin management to outpatients who visited McCormick hospital, Chiang Mai, Thailand. Comparison of pre- and post-counseling service conducted over a period of 5 months. The outcomes were international normalized ratio (INR) control (therapeutic efficacy), warfarin-related complications and adverse events (safety), patients' knowledge and satisfaction regarding warfarin. The data were collected from 26 outpatients who were prescribed warfarin. There were 16 patients (64.0%) who received pre-counseling service had out-of-range INR. There were 14 patients (87.5%) had sub-therapeutic INR. The analysis of INR control within the therapeutic range was not statistically different between pre- and post-counseling services (p=0.062). Thromboembolic complications were found in 4 patients (15.4%) and bleeding complications were found in 3 patients (11.5%) during pre-counseling period. Interestingly, thromboembolic and bleeding complications were not detected after post-counseling services (0%). Before receiving counseling service, the most 3 incorrect answers on warfarin knowledge were the effect of a missing dose and its management, the benefit of INR monitoring and the possible adverse effects of sub-therapeutic INR. Patient's knowledge on warfarin among participants significantly increased after receiving counseling services (p<0.001). In addition, all participated outpatients satisfied with pharmacist counseling services. Taken together, this study demonstrated that pharmacist's counseling could improve warfarin-associated complications, warfarin knowledge and patient's satisfaction in pharmacy's ambulatory care.

Keywords: warfarin, pharmacists' counseling, complications, knowledge, satisfaction

บทคัดย่อ: การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลการให้คำแนะนำของเภสัชกรแก่ผู้ป่วยนอกที่รับประทานยาวาร์ฟารินที่โรงพยาบาลแมคคอร์มิค จังหวัดเชียงใหม่ โดยจะทำการเปรียบเทียบผลก่อนและหลังการให้คำแนะนำของเภสัชกรกับผู้ป่วยในช่วงระยะเวลาที่ทำการศึกษา 5 เดือน จะศึกษาผลการให้คำแนะนำของเภสัชกรต่อการควบคุมระดับ INR (ประสิทธิภาพ) การเกิดภาวะแทรกซ้อนจากการใช้ยาวาร์ฟาริน (ความปลอดภัย) ความรู้ความเข้าใจเกี่ยวกับยาวาร์ฟาริน และความพึงพอใจต่อการได้รับคำแนะนำจากเภสัชกร ผู้ป่วยนอกที่ได้รับยาวาร์ฟารินจำนวน 26 คน ก่อนการให้คำแนะนำผู้ป่วยร้อยละ 64.0 มีระดับ INR อยู่นอกช่วงของการรักษาที่ต้องการ ซึ่งผู้ป่วยส่วนใหญ่ (ร้อยละ 87.5) มีระดับ INR อยู่ต่ำกว่าช่วงของการรักษา การให้คำแนะนำโดยเภสัชกรไม่มีความสัมพันธ์กับการมีค่า INR อยู่ในช่วงเป้าหมายอย่างมีนัยสำคัญ (p=0.062) อย่างไรก็ตามพบว่าก่อนการให้คำแนะนำผู้ป่วย 4 คน (ร้อยละ 15.4) เกิดภาวะแทรกซ้อนที่ทำให้เกิดลิ่มเลือดอุดตัน และผู้ป่วย 3 คน (ร้อยละ 11.5) เกิดภาวะแทรกซ้อนที่ทำให้เกิดเลือดออก หลังจากได้รับคำแนะนำแล้วไม่พบผู้ป่วยที่เกิดภาวะแทรกซ้อนเลย ก่อนการให้คำแนะนำพบว่าความรู้เกี่ยวกับยาวาร์ฟารินที่ผู้ป่วยตอบผิดมากที่สุด 3 ลำดับแรก คือ ข้อควรปฏิบัติหากลืมรับประทานยาวาร์ฟาริน ประโยชน์ของการเข้ารับการติดตามค่า INR และอาการไม่พึงประสงค์ที่อาจเกิดขึ้นเมื่อค่า INR ต่ำกว่าเป้าหมาย โดยผู้ป่วยมีความรู้ความเข้าใจเกี่ยวกับยาวาร์ฟารินเพิ่มขึ้นหลังจากได้รับความรู้เกี่ยวกับยาวาร์ฟารินอย่างมีนัยสำคัญ (p<0.001) และพบว่าผู้ป่วยทุกคนมีความพึงพอใจจากการได้รับคำแนะนำจากเภสัชกร ดังนั้นการให้คำแนะนำของเภสัชกรช่วยป้องกันการเกิดภาวะแทรกซ้อนจากการใช้ยาวาร์ฟาริน อีกทั้งยังทำให้ผู้ป่วยมีความรู้ความเข้าใจเกี่ยวกับยาวาร์ฟาริน และมีความพึงพอใจต่อการบริบาลเภสัชกรรมมากขึ้นด้วย

คำสำคัญ: วาร์ฟาริน, บริบาลเภสัชกรรม, ภาวะแทรกซ้อน, ความรู้ความเข้าใจ, ความพึงพอใจ

INTRODUCTION

Warfarin is a widely used oral anticoagulant for the prevention and treatment of pulmonary embolism, venous thrombosis, myocardial infarction, and atrial fibrillation (Shrestha *et al.*, 2015; Shuaib *et al.*, 2014). It has a narrow therapeutic window (Kuruvilla and Gurk-Turner, 2001). Moreover, various factors have been reported to affect the response to warfarin therapy such as older age, disease states, warfarin dose, and drug-drug interaction (Abdel-Aziz *et al*., 2015). Warfarin therapy in outpatient setting requires the close monitoring because it has been reported with the complications especially clotting and bleeding (Kuruvilla and Gurk-Turner, 2001; Shrestha *et al.*, 2015). Pharmacists who have the knowledge on warfarin pharmacokinetics and drug interactions can assist the patients to maintain effective and safe anticoagulation. Successful anticoagulation implies lower incidences of complications and number of patients with out-of-range INR (Lakshmi *et al*., 2013; Stafford *et al*., 2011). The desired outcomes and low incidences of adverse drug reactions can be accomplished by providing the knowledge of warfarin and adherence to warfarin (Shrestha *et al*., 2015). Thus, patient counseling is very important in order to maintain the international normalized ratio (INR) within the target range (Kuruvilla and Gurk-Turner, 2001), decrease the incidence of warfarin-associated complications (Chilipko and Norwood, 2014; Lakshmi *et al*., 2013), improve the patients' knowledge and satisfaction (Tang *et al*., 2003; Waterman *et al*., 2001).

Previous studies emphasized that clinical pharmacists play an important role in improving the overall therapeutic outcomes (Krittathanmakul *et al*., 2006; Chilipko and Norwood, 2014; Lakshmi *et al*., 2013; Tang *et al*., 2003). Therefore, this study aims to determine the effects of the pharmacists' outpatients counseling on the therapeutic efficacy, warfarin-associated complications, patient knowledge and satisfaction.

MATERIALS AND METHODS

Study design and setting

It was a prospective cohort, single center study conducted over a period of 5 months. The study was carried out at the Cardiac Care Unit, McCormick hospital, Chiang Mai, Thailand. This study got the ethical clearance from Human Experimentation Committee, Research Institute for Health Sciences (RIHES), Chiang Mai University, Chiang Mai, Thailand. Written informed consent was obtained from all participants.

Study population and data collection

Based on sample size calculation, approximately 40 patients were estimated as being statistically adequate. Participants were selected using the purposive sampling of outpatients who were prescribed warfarin and had been taking warfarin for at least 1 months. Patients who refused to participate in this study were excluded.

A face to face interview was carried out using a validated questionnaire to assess the patient's knowledge on warfarin and patient's satisfaction. The questionnaire had acceptable content validity, reliability and consistency (Cronbach alpha=0.88). Three experts agreed that the questions were relevant to evaluate warfarin knowledge. Patient's knowledge part consists of 10 questions including indications of warfarin, how to take warfarin, do's and don'ts, the effect of a missing dose and its management, the possible adverse effects of warfarin, the advantages of INR monitoring, self-monitoring for both thromboembolic and bleeding complications, drug interactions including drug-drug, drug-food and drug-herb interactions. Scores 1 and 0 were given for each right and wrong answer, respectively. Patient's satisfaction part consists of 1 yes-no question. Characteristics of the patients,

indications of warfarin, patient's comorbidity, target INR, dosage and duration of warfarin, drug interaction, adverse drug reactions, and complications were collected from medical chart. Pre-counseling period, the data were collected as a baseline INR, complications, knowledge on warfarin and satisfaction. Patients were counseled by the pharmacists. Post-counseling period, the data were collected again using the same questionnaire when the patients came for the following visit (no greater than 3 months).

Process of pharmacist counseling

Licensed pharmacists provided the face-to-face counseling about an hour for each patients who visited anticoagulation clinic. At the initial visit to anticoagulation clinic as a pre-counseling period, patients who fulfilled the inclusion criteria were invited to participate in the study. Pharmacists monitored INR results and physical examination to evaluate the efficacy and complications regarding anticoagulation therapy. Pharmacists also determined patients' baseline knowledge on warfarin and counseling satisfaction using the validated questionnaire, via verbal query. The counseling included the indications of warfarin, how to take it, do's and don'ts, the effect of a missing dose and its management, the possible adverse effects of warfarin, the advantages of INR monitoring, self-monitoring for both thromboembolic and bleeding complications, drug interactions including drug-drug, drug-food and drug-herb interactions. The following visit (no greater than 3 months) as a post-counseling period, pharmacists assessed for possible complications such as bleeding symptoms and thromboembolic signs. Patients were routinely monitored INR results and physical examination. They were also determined their knowledge regarding warfarin and counseling satisfaction.

Statistical analysis

Descriptive statistics were used to calculate baseline characteristics of the patients. Data were shown as number (%) of patients and mean ± SD. The number of patients whose INR was in therapeutic range, the number of patients who experienced any adverse events and complications, patients' knowledge and satisfaction between pre- and post-counseling service were compared. Paired t-test and McNemar's test were used as appropriate and used based on the normal distribution of the data from the populations which are distributed normally. A p-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Twenty six patients enrolled in this study, the mean age was 62.9±14.8. Of the study population, 16 patients (61.5 %) were male. Twenty (87.0%) patients had ≥1 comorbidities whereas 13.0% of them had no comorbidity as shown in Table 1. Most of patients (34.1%) had chronic heart failure as the comorbidity followed by hypertension (29.5%) and thyroid disorders (9.1%). Most of them (61.5%) used to be counseled by the pharmacists about an anticoagulation drug therapy. Only 2 patients (7.7%) experienced drug-drug interaction (warfarin-isoniazid; level 3 moderate and warfarin-rifampin; level 2 major) and drug-supplement interaction (warfarin-fish oil; level 2 major) (Ansell *et al*., 2008) (Table 1).

Most common indication for anticoagulation was found to be the atrial fibrillation (61.3%) followed by the mitral valve replacement (12.9%) and myocardial infarction (6.5%) as shown in Table 1. Majority of patients (88.5%) had the target INR 2.0-3.0 whereas 11.5% of them had the target INR 2.5-3.5 (Table 1).

Table 1. Baseline characteristics of the patients (n=26)

Characteristics	Number of patients (%)
Gender	
- Male	16 (61.5)
- Female	10 (38.5)
Mean age (years ± SD)	62.9±14.8
Comorbidities[a]	
- No comorbidity	3 (13.0)
- ≥1 comorbidities	20 (87.0)
Pattern of patients' comorbidity[b]	
- Chronic heart failure	15 (34.1)
- Hypertension	13 (29.5)
- Thyroid disorders	4 (9.1)
- Dyslipidemia	2 (4.5)
- Diabetes mellitus	2 (4.5)
- Others	6 (18.2)
Indications for anticoagulation[c]	
- Atrial fibrillation	19 (61.3)
- Mitral valve replacement	4 (12.9)
- Myocardial infarction	2 (6.5)
- Others	6 (19.4)
Baseline INR (target INR)	
- 2.0-3.0	23 (88.5)
- 2.5-3.5	3 (11.5)
Used to be counseled by the pharmacists	
- Yes	16 (61.5)
- No	10 (38.5)
Herbal intake	
- Yes	2 (7.7)
- No	24 (92.3)
Dietary supplement intake	
- Yes	4 (15.4)
- No	22 (84.6)
Drug-drug interactions	
- Yes	2 (7.7)
- No	24 (92.3)
Smoking	
- Yes	1 (3.8)
- No	25 (96.2)
Alcohol consumption	
- Yes	0 (0.0)
- No	26 (100.0)

[a] n=23

[b] One patient might have more than 1 comorbidity

[c] More than 1 indication might be found in 1 patient

Sixteen patients (64.0%) who received pre-counseling services had out-of-range INR. Most of them (87.5%) had sub-therapeutic INR. Post-counseling period, 11 patients (52.4%) had out-of-range INR and all of them had sub-therapeutic INR. The analysis about

controlling INR in the therapeutic range was not statistically different between before and after counseling services (p=0.062) as shown in Table 2. This finding is consistent with previous studies that there was no significant relationship between INR control and patients' knowledge on anticoagulation (p=0.676) (Krittathanmakul *et al*., 2006; Baker *et al*., 2011).

Table 2. Analysis of INR control in patients during pre- and post-counseling period

	Number of patients (%)		*p-value**
	INR in therapeutic range	INR out of therapeutic range	
Pre-counseling	9 (36.0)	16 (64.0)	0.062
Post-counseling	10 (47.6)	11 (52.4)	

*****McNemar's Test

During pre-counseling period, thromboembolic complications were found in 4 patients (15.4%) and bleeding complications in 3 patients (11.5%). Interestingly, there were not both thromboembolic and bleeding complications after receiving counseling services (0%) which was consistent with previous studies (Table 3). The study showed that the number of patients experiencing adverse events was lower in pharmacist-managed group (p=0.015) comparing to the usual care group (Locke *et al*., 2005). Another study showed the effectiveness of pharmacist-managed service in the decrease of hospitalization rates and emergency department visits, reduced by 56% versus nurse-managed service and 61% versus usual care ($p<0.01$) (Rudd and Dier, 2010). Moreover, another study also showed that thromboembolic events significantly decreased in pharmacist-monitored group (p=0.01) (Poon *et al*., 2007).

Table 3. Adverse drug reactions including complications in patients during pre- and post-counseling period

Adverse drug reactions	Number of patients (%)	
	Pre-counseling	Post-counseling
Thromboembolic complications		
- Yes	4 (15.4)	0 (0.0)
- No	22 (84.6)	21 (100.0)
Bleeding complications		
- Yes	3 (11.5)	0 (0.0)
- No	23 (88.5)	21 (100.0)

Patient's baseline knowledge was assessed by validated questionnaire. Mean baseline knowledge score was 5.8 ± 2.1 (Table 4). The most 3 incorrect answers on warfarin knowledge were the effect of a missing dose and its management (80.8%), the advantage of INR monitoring (76.9%) and the possible adverse effects of outpatients who had sub-therapeutic INR (73.1%). Post-counseling period, the knowledge on warfarin was reassessed and mean score increased to 7.3 ± 2.4 (Table 4). The most 3 incorrect answers on warfarin knowledge were the advantage of INR monitoring (61.9%), the effect of a missing dose and its management (52.4%) and the possible adverse effects of outpatients who had sub-therapeutic INR (38.1%). This study proved that patient's knowledge on warfarin significantly improved after counseling by clinical pharmacists ($p<0.001$) as shown in Table 4. Our result is consistent with previous study which showed the statistically significant improvement in patients' warfarin knowledge after pharmacists' counseling (Krittathanmakul *et al*., 2006; Collins *et al*. 2014).

Table 4. Analysis of warfarin knowledge in patients during pre- and post-counseling period

	Warfarin knowledge score (mean ± SD)	*p-value**
Pre-counseling	5.8 ± 2.1	<0.001
Post-counseling	7.3 ± 2.4	

*Paired sample *t*-test

Patient knowledge is the very important key in order to take warfarin effectively and safely. There was a trend toward lower number of patients who had out-of-range INR during post-counseling period, but the expected differences between pre- and post-counseling did not reach a level of statistical significance. Remarkably, we found a positive relationship between the pharmacists' counseling service and the incidence of warfarin-associated complications. Our finding is consistent with previous studies. They showed that the patient's knowledge on oral anticoagulation was improved after counseled by the pharmacists. Moreover, patients also achieved the better therapeutic outcome. Previous studies emphasized that clinical pharmacists play an important role in improving the overall therapeutic outcomes (Chilipko and Norwood, 2014; Lakshmi *et al*., 2013; Tang *et al*., 2003). Another study showed that pharmacist's counseling through verbal and written reinforcement could improve patients' knowledge on warfarin. They might be able to identify the complications related to the anticoagulation therapy, particularly minor bleeding. Pharmacist's counseling might be the factors that could affect the control of INR and warfarin-associated complications (Krittathanmakul *et al.*, 2006).

Assessment of patient's satisfaction with the anticoagulation service was carried out using the questionnaire (yes-no question). The results showed that all the patients (100.0%) were satisfied with the pharmacists' counseling services. Our finding is consistent with the previous study which showed the improvement of patients' satisfaction with the knowledge about antithrombotic therapy after receiving a telephone-based anticoagulation service by their physician or the multidisciplinary (Waterman *et al*., 2001). Moreover, another study showed that patient satisfaction toward pharmacist's counseling service was rated as good in many areas due to patient's health perception (Krittathanmakul *et al*., 2006).

Limitations

The power of the study was limited due to the small sample size and short time period. This study was also conducted at a single center. These factors might affect the generalizability of the results. Further study using a larger sample size and longer time period should be performed. In addition, multicenter study might increase the power of the future work.

CONCLUSION

Anticoagulation therapy especially warfarin has a problematic challenge for both patients and health care professionals. Our finding highlighted that pharmacist's counseling plays an important role in achieving the desired therapeutic outcomes while preventing warfarin-associated complications. In addition, warfarin knowledge and patient's satisfaction improve after counseled by the pharmacists. It could be implied that patient's knowledge on warfarin improved therapeutic outcomes and medication safety in pharmacy's ambulatory care. Multidisciplinary team is also a key in order to dispense warfarin effectively and safely.

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