

Anticoagulation with Warfarin: Roles of Adherence, Social Support and Illness Perception

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ABSTRACT

Objectives: This study was aimed to determine (1) the associations between adherence to warfarin, social support, perception of illness, and demographic factors on the quality of international normalized ratios (INRs); as well as (2) the relationship between the patients' scores in the Malaysian medication adherence scale (MALMAS) and their current INRs.

Method: This cross-sectional survey was conducted from November 2017 to January 2018 at the warfarin clinic of Jerantut Hospital, Malaysia.

Results: Some 58 participants were recruited, of whom 70.7% were diagnosed with atrial fibrillation (AF). Overall, 87.9% of the participants claimed adherence to their warfarin regimens. Patients with good-quality INR therapy were significantly older, had a higher median income and longer appointment durations. In terms of illness perception (IP), participants with good-quality INR therapy had significantly lower scores in the identity, personal control, and consequence domains. Overall, the total scores for IP were significantly lower in the good-quality INR therapy. Meanwhile, the MALMAS scores were significantly lower in patients with sub-therapeutic current INR. However, there were no associations between warfarin adherence and perceived social support with current TTR.

Conclusion: Monitoring of demographic factors and IP's domains is vital since they were associated with quality of INR therapy. Meanwhile, the occurrence of sub-therapeutic current INR should raise suspicion of poor adherence in these patients. Overall, IP and MALMAS are useful tools that should be integrated into the patient care protocols.

Keywords: Warfarin, adherence, illness perception, social support, time in therapeutic range

INTRODUCTION

Today, pharmacists have become actively involved in patient monitoring and warfarin-prescribing [1]. Warfarin is used in the treatment of various thromboembolism-related disorders [2] but owing to its narrow therapeutic index, regular international normalized ratio (INR) monitoring is required. This is vital for (1) patients' safety in term of preventing complications like minor-to-severe bleeding in light of over-anticoagulation [2], and (2) ensuring treatment efficacy by avoiding sub-therapeutic INR due to insufficient dosing[2].

In the current settings, physicians and pharmacists usually prescribe clinical follow-ups ranging from three days (in unstable patients) to three months (in stable patients) and dose adjustments are made based on a normogram provided by the Malaysian Ministry of Health [3].

The duration of warfarin treatment ranges from a few months to lifelong [2] and healthcare practitioners are aware that the achievement of prolonged time in therapeutic range (TTR) is a key objective of the treatment [2]. Hence, a good motivation and long-term commitment from both patients and caregivers in terms of adherence to follow-ups and lifestyle changes such as diet restriction as well as warfarin intake is needed [4].

While the associations between social support and TTR have rarely been explored, yet variations in relationships between warfarin adherence(4,5,15) and illness-perception (IP)(6,26) with TTR have been reported in different studies making their findings difficult to be generalized for clinical practices. Thus in current study, we aimed to determine the relationships between adherence to warfarin with TTR and current international normalized ratio (INR) and also the relationships between social support and IP on TTR.

METHOD

This cross-sectional survey was conducted at the warfarin clinic of Jerantut Hospital, Malaysia from November to December 2017. It was approved by the Medical Research and Ethics Committee (MREC) (registration number: NMRR-17-2036-37528). Convenience sampling was performed, and written consent was obtained from the potential respondents prior to the survey. Participants who were at least 18 years of age, able to give consent, and on warfarin for at least six months were recruited. Those who refused to participate, or had language barriers, speech/ hearing disabilities, mental disorders, and histories of defaulting treatment were excluded. The researchers spent between 20 and 30 minutes to conduct the survey on each patient during warfarin clinic days.

In the pilot study, the Malay-version Malaysian Medication Adherence Scale (MALMAS) [7] scores of 30 adherent (TTR > 60%) and non-adherent (TTR < 60%) patients were normally distributed with a standard deviation of 0.8. Meanwhile, the true difference between both groups' means was 0.5. With

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reference to this, 41 subjects were needed for the adherent and non-adherent groups respectively to achieve a study power of 80%. Also, the Type I error in this test was set at 0.05.

MALMAS [7], Multidimensional Scale of Perceived Social Support (MSPSS-M) [8], and illness perception (IP) [9] questionnaires were used to assess warfarin adherence, social support, and IP respectively. Demographic data was obtained verbally from the patients, while six-to-twelve-month INR histories were extracted from participants' INR booklets.

MALMAS consisted of eight questions. The first item of the MALMAS contained five possible responses: (1) all the time, (2) often, (3) sometimes, (4) rarely, and (5) never. The remaining seven items had dichotomous yes-no responses options. Items two to four and six to eight were reverse coded (i.e. "no" = 1, "yes" = 0), while the converse was true for item five ("no" = 0, "yes" = 1). The first item had five negatively scored response options that ranged from zero (all the time) to one (never). The total MALMAS score, which ranged from 0 to 8, was used to assess the patients' medication adherence one month prior to the administration of the questionnaire [7]. Patients whose scores were less than six were categorized as non-adherent.

MSPSS-M comprised of 12 questions whose scores ranged from one to seven marks each. Hence, the total mark ranged from seven to 84. Questions 1, 2, and 10 evaluated the patients' perceptions of support from their significant others, questions 3, 4, 8, and 11 family members, and questions 6, 7, 9, and 12 friends [8,10]. Higher score reflected better social support.

The Malay version of IP was validated on the hypertensive population in Malaysia, and the Cronbach's alpha was found to be 0.65. This questionnaire consisted of eight questions, each of which was scored between zero and ten. Ergo, this questionnaire had a maximum total mark of 80. The questions on personal control (question 3), treatment control (question 4), and understanding of illness (question 7) were reverse-scored, whereby lower scores indicated a less negative view of the illness. Conversely, higher overall scores indicated more negative view of the illness [9]. Time in therapeutic range (TTR) was measured using the Rosendaal formula [11, 12], whereby participants who had a TTR of > 60% were considered to have achieved good quality INR control [13,14,29,30].

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 18.0 software. Chi-square test was employed to analyze the categorical variables and T-test or Mann Whitney U test was used to determine the relationships between the categorical and numerical variables. The outcomes of the continuous variables were expressed as means \pm standard deviations (SDs), or medians and interquartile ranges (IQRs) where applicable. A P-value of < 0.05 was considered to be statistically significant.

RESULTS

Participants' characteristics

As of December 2017, 75 patients have attended the warfarin clinic at Jerantut Hospital, all of whom were approached to solicit their participation in the survey. However, nine were excluded owing to language barriers, six on treatment for less than six months, and two with histories of defaulting treatment in the past year. The remaining 58 patients agreed to participate in the survey, hence giving a power of 65%.

In the current survey, 48.3% (n = 28) of the participants were males, and the median age was 63.5 years (IQR: 16.3). The majority of the respondents (70.7%; n = 41) were diagnosed with atrial fibrillation (AF) and received warfarin for a median of 41.5 months (IQR: 80.0). For the past six to 12 months, the median follow-up interval was once every 27 days (IQR: 19) and the mean warfarin daily dose of 2.5 ± 1.2 mg per day.

Overall, 87.9% (n = 51) of the participants claimed adherence to their warfarin regimens. For IP, participants scored the highest in the timeline- (median: 9; IQR: 4.3) and illness-specific (median: 9; IQR: 2) domains. Overall, mean total IP score was 35.1 ± 8.1 . As for social support, the median scores for spousal- and friend-support were both 20 (IQR: 9 and 5 respectively). The mean scores for family support and total social support were 23.7 ± 3.6 and 65.3 ± 11.3 respectively. These data are presented in Table 1.

Characteristic differences between patients with good and poor quality INR control

In terms of demographic factors, it was noted that patients with good quality INR control were older (median age: 68 years; IQR: 18) than their poor quality INR control counterparts (median age: 50 years; IQR: 22) (P = 0.013). The former group also recorded a higher median income (Malaysian Ringgit/ MYR 1 000; IQR: 1300) vis-a-vis the latter group (MYR 300; IQR: 1310). Patients with good INR control were under longer follow-up intervals (median: 42 days; IQR: 20) than poor quality INR control ones (median: 24 days; IQR: 6) (P = 0.001). However, duration on warfarin treatment and daily warfarin dose had no significant association with INR control. Good INR control group had lower scores in the following domains: identity (median: 3.0 vs 4.5; IQR: 5.5 vs 4.0; P = 0.039), personal control (median: 2.0 vs 3.0; IQR: 2.0 vs 2.0; P = 0.047), consequences (median: 1.5 vs 3.0; IQR: 3.0 vs 4.8; P = 0.016). Likewise, the total IP score was significantly lower in patients with good INR control (median: 32.1; IQR: 7.5) as compared to those with poor INR control (median: 37.5; IQR: 8.0) (P = 0.012). Other IP and perceived social support domains did not have a significant influence on INR control (Table 2).

Relationship between MALMAS and current INR readings

As shown in Figure 1, patients who managed to maintain the target INR for the past four to six weeks had significantly higher MALMAS scores (median: 8.0; IQR: 1.0) than their counterparts who failed to do so (median: 7.0; IQR: 2.0) (P = 0.022).

DISCUSSION

In addition to the relationship between MALMAS scores and current INR readings, this was the first study that investigated the associations between medication adherence, social support, and illness perception with INR control.

Roles of TTR

TTR lower than 60% increased risks of bleeding [12,13] yet its associations with stroke and systemic embolism varied between different studies [12,13,14]. A study between subgroups of patients with TTRs of 60 to 75% versus those that exceeded 75% found that the risks of major bleeding, mortality, and stroke were not significantly different between the two groups [14]. Thus the choice of using the TTR value of 60% and above as an indication of good quality INR therapy [29,30].

Associations between demographic factors and warfarin therapy on TTR

Our findings supported the associations between advanced age and higher income on quality of INR therapy [17,18]. The importance of good quality INR therapy in lower-income patients should not be underestimated since the failure to achieve the same will ultimately result in higher risks of haemorrhage and death [19].

Predictably, those with poor quality INR control had significantly shorter follow-up intervals (i.e. time between follow-up sessions) as compared to patients with good quality INR control. In this study, patients who achieved good quality INR had their appointments once every 42 days, which was much longer than that of their overseas counterparts (21 – 24 days) [20]. On the contrary, patients with lower TTRs had their appointments scheduled more frequently, i.e. once in every three weeks or so. Hence, this could be an indication that shorter follow-up intervals should be considered in patients with poor quality INR in current setting.

Adherence

Multiple tools have been used to determine warfarin adherence such as pill counts, medication event monitoring systems (MEMS), and self-reported questionnaires [4,5,12,15,21,22]. Nonetheless, self-reported adherences varied between studies depending on the assessment tools used [4,5,12,15,22]. A frequently-utilized questionnaire for the evaluation of medication adherence is the eight-item modified Morisky medication adherence scale (MMAS-8) [4,5,12]. From there, a new questionnaire has been developed by Malaysian researchers, and it was named "Malaysian medication adherence scale" (MALMAS) [7].

Adherence and TTR

Despite the high adherence to warfarin (about 88%) in this study, only around 45% of the patients achieved good quality INR control. Nonetheless, this figure was still slightly higher than the 15% to 35% in other studies [4,5]. It should be noted that comparisons are difficult since those studies have used

higher cut-off points of 70% and 75% for defining therapeutic TTR [4,5]. Also, lack of clear correlation between self-reported adherence and TTR is not uncommon probably due to different TTR calculations and therapeutic TTR definitions [4,5,15].

Even though a recent study has reported that warfarin adherence was related to TTR [5] yet other research have found that only 26% to 35% of patients managed to achieve a TTR of more than 75% despite the presence of self-reported adherence levels of up to 46% to 48% [4,15]. Nevertheless, this observation was not unexpected owing to the fact that MMAS-8 had limited recall period of two weeks only [4]. This was supported by our finding that higher MALMAS scores were only predictive of current INR readings but not TTR. Likewise, previous studies have shown that adherence measurement tools like the visual analogue scale (VAS) and 7-day recall test were more predictive of short-term INR changes [22]. Other tool such as MEMS have revealed that good adherence within the past 12 months was associated with good TTR [23] yet this device is far too costly to be routinely used in daily clinical practice [21]. Based on this finding, monitoring of adherence should essentially comprise the administration of self-reported questionnaires such as MALMAS at every visit, along with an emphasis on warfarin adherence in patients with poor quality INR control.

Social support and TTR

In hypertensive patients, medication-adherence counselling and treatment optimization by pharmacists have led to improvements in social support and blood pressure. Nevertheless, the effect of social support on blood pressure was insignificant [24].

Based on a previous study [24], it was expected that social support did not markedly differ between the poor and good quality INR control groups. This was due to the fact that the participants of this research were managed (in terms of warfarin dosing, warfarin adherence, and lifestyle modification counselling) by trained pharmacists at every visit. This indicates that one of the most important outcomes of social support is to retain patients within the care system and hence, avoid complications that are attributable to their illnesses [25].

IP and TTR

IP has been explored in warfarin-taking patients prior to switching treatment to novel oral anticoagulants (NOACs) [6] as well as its changes upon receiving educational interventions [26].

It was reported that IP did not predict TTR changes among 46 and 51 participants whom underwent educational interventions and the usual care respectively [26]. However, this could be attributed to the fact that IP was only assessed in 27 participants. On the contrary, a study on 148 AF or venous thromboembolism (VTE) has found that the scores for the consequence and timeline (cyclical) domains were significantly

higher in patients whose TTRs were less than 50% as compared to those whose TTRs exceeded 75% [6]. Meanwhile timeline (acute chronic) and illness coherence domains scores were significantly lower in the former group relative to the latter group [6]. Evidently, the only similarity between this research and the aforementioned one [6] was the significantly higher consequence domain scores in patients with good quality INR control vis-à-vis those with poor quality INR control. Apart from that, patients with shorter TTRs had higher scores in the identity domain, thereby denoting a more negative effect of the illness on their lives.

IP interacts with several factors like adherence to medications and lifestyle modifications. For instance, improved treatment control had a positive impact on medication adherence in hypertensive patients [27]. Apparently, good medication adherence in diabetic patients has resulted in better outcomes and personal control scores than their poorly compliant counterparts [28]. In this study, it was likely that the long-term maintenance of self-management in terms of diet control [16] and medication adherence [21] has helped the participants to achieve good quality INR control, which in turn produced better outcomes and personal control scores.

With the assumption that IP was a better indicator of long-term anticoagulation control (based on the poorer IP in patients with lower TTRs), IP-related interventions should be held during patients' encounters. Since educational interventions might not improve the IP [26], different approaches – like exploring issues and providing solutions from the IP's point of view – might be better mechanisms for patients to adapt to their illnesses [28].

Strength and limitations

This was the first study that investigated the relationships between TTR and INR with the newly developed MALMAS questionnaire in patients prescribed with warfarin. Current finding has also provided preliminary evidence that current INR readings was associated with MALMAS scores. However, this study was not without limitations. The sample size was rather small and inadequately powered due to the small numbers of patients diagnosed with heart-related conditions within this locality that required them to receive warfarin treatment.

CONCLUSION

To improve the quality of INR therapy in patients receiving warfarin, a multifaceted approach which addresses essential factors like medication adherence, social support, and patients' perceived severity of their illnesses has to be implemented. Ideally, warfarin adherence assessments should be performed during every follow-up session, along with periodical evaluations of illness perceptions.

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Table 1. Participants' characteristics

Characteristics	Population (N=58)
Age (years)	63.5(16.3)
Male gender (n,%)	28(48.3)
Income (RM)	950(1950)
Diagnosis (n,%)	
AF	41(70.7)
Others	17(29.3)
Duration on warfarin treatment (months)	41.5(80.0)
Appointment length (days)	27(19)
Daily dose (mg) ^a	2.5(1.2)
TTR control	
>60%	26(44.8)
<60%	32(55.2)
Adherence (n,%)	
Adherent	51(87.9)
Nonadherent	7(12.1)
Illness perception	
Identity	3.5(5.3)
Timeline	9.0(4.3)
Personal control	3.0(1.0)
Treatment control	2.5(2.0)
Consequence	3.0(4.0)
Illness concern	9.0(2.0)
Illness coherence	3.0(3.0)
Emotional response	4.0(5.3)
Total illness perception score ^a	35.1(8.1)
Social support	
Spousal	20.0(9.0)
Family ^a	23.7(3.6)
Friends	20.0(5.0)
Total social support ^a	65.3(11.3)

Data are shown as median (IQR) except where indicated

^aData are shown as mean (SD)

Table 2. Factors influencing TTR

	TTR>60%	TTR <60%	P
Age (years)	68(18)	59(22)	0.013
Income (RM)	1000(1300)	300(1310)	0.020
Duration on warfarin treatment (months)	68(105)	38(48)	0.149
Appointment length (days)	42(20)	24(6)	0.000
Daily dose (mg) ^a	2.3(1.0)	2.7(1.2)	0.170
Illness perception			
Identity	3.0(5.5)	4.5(4.0)	0.039
Timeline	9.0(5.0)	9.0(2.8)	0.489
Personal control	2.0(2.0)	3.0(2.0)	0.047
Treatment control	2.5(2.0)	2.5(1.0)	0.406
Consequence	1.5(3.0)	3.0(4.8)	0.016
Illness concern	9.0(2.0)	8.0(1.8)	0.204
Illness coherence	3.5(3.0)	2.5(3.0)	0.441
Emotional response	3.0(6.0)	5.5(5.0)	0.106
Total illness score ^a	32.1(7.5)	37.5(8.0)	0.012
Social support			
Spousal	21.0(9.0)	20.0(10.5)	0.893
Family ^a	23.9(4.0)	23.5(3.1)	0.628
Friends	20.5(7.3)	20.0(4.3)	0.682
Total social support ^a	65.6(12.2)	65.0(10.6)	0.828
Adherence (n,%) ^b			0.116
Adherent	25(96.2)	26(81.3)	
Non-adherent	1(3.8)	6(18.7)	

Data are shown as median (IQR) except where indicated

^aData are shown as mean (SD)

^bData reported using Fisher's Exact test