Patient adherence to warfarin therapy and its impact on anticoagulation control

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Abstract Warfarin is a commonly prescribed oral anticoagulant in Saudi Arabia and yet patient adherence to warfarin therapy and its impact on anticoagulation control have not been well researched here. A cross-sectional survey was conducted over 6 weeks at the outpatient anticoagulant clinic on patients who were receiving warfarin. Adherence was assessed using the translated Arabic version of the Morisky Medication Adherence Scale (MMAS-8). Levels of adherence were classed as low (score ≤ 7), or high (score = 8) based on the scores. Good anticoagulation control was defined as percent Time INR in Therapeutic Range (TTR) ≥ 75% using the Rosendaal method. A total of 192 patients completed a questionnaire with a response rate of 68.1%. It was established that no association was found between adherence to warfarin therapy and INR control groups. Among the 89 (46.4%) patients who had high adherence, only 34 (38.2%) had an acceptable INR control. This was versus 103 (53.6%) patients who had low adherence but also 34 (33.0%) had good INR control. Multivariate logistic regression (MLR) analysis showed that when studying females and occupational status of unemployment, they were independently associated with poor INR control with an OR 2.31, 95% CI 1.10–4.92, and OR 2.71, 95% CI 1.12–6.61 respectively. MLR analysis also showed that age < 50 years alongside no formal education was independently associated with low adherence to warfarin therapy with an OR 2.67, 95% CI 1.29–5.52 and OR 2.63, 95% CI 1.01–6.93 respectively. The demographic background influences adherence and INR control, but no association was found between adherence and anticoagulation control.

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1. Introduction

Poor adherence to medication use is one of the greatest challenges for the improvement of health outcomes (World Health Organization, 2003). Non-adherence to medications is ongoing as patients receive more medications to treat their chronic medical conditions. This is also apparent in the elderly population due to a decline in their mental and physical health (Gurwitz et al., 2003). The outcome of poor adherence to medications can be life threatening with certain drugs like warfarin
which has very narrow therapeutic index (Woodwell and Cherry, 2004). The drug is used as a long-term oral anticoagulant to prevent thromboembolic complications of various conditions including stroke; atrial fibrillation; venous thromboembolism; and valvular heart disease (Rose et al., 2009; Wysowski et al., 2007). Warfarin is effective when the therapeutic range is maintained, but when the levels are below or above the intended range, it is associated with increased risk of thrombosis and bleeding, respectively (Hylek et al., 1996).

Poor adherence to warfarin is common with one in five doses taken incorrectly even in the setting of a dedicated anticoagulation clinic (Platt et al., 2010). A study showed that up to 92% of the patients could not adhere to warfarin therapy and had under anticoagulation control. For each 10% increase in non-adherence to warfarin, there was a 14% increase in the risk of under-anticoagulation and caused significantly higher rates of morbidity and mortality (Kimmel et al., 2007). An older age, low level of education status and unemployment status were seen to be independent risk factors for nonadherence to warfarin therapy (Cruess et al., 2010).

Several studies have demonstrated that in patients on chronic warfarin therapy, adherence is one of the many factors that can affect anticoagulation control. Davis et al. concluded in their study that adequate adherence, as determined by the Morisky survey, was significantly associated with anticoagulation control (Davis et al., 2005).

An association between patients’ adherence and anticoagulation control has not been well researched in Saudi Arabia. The study objective was to assess patient adherence to warfarin treatment using the MMAS-8 Arabic translated version, anticoagulation control, and the association between adherence and anticoagulation control. It will also help to identify factors associated with poor adherence and anticoagulation control. This study should help us to identify deficiencies and opportunities for strategic initiatives to improve medication adherence and INR control. It will be an imperative step toward optimizing the anticoagulation care at our clinic.

2. Materials and methods

This cross-sectional study was conducted in an outpatient anticoagulation clinic of King Khalid University hospital in Riyadh, Saudi Arabia. This was after receiving the institutional review board of approval. The hospital is a tertiary care hospital with a 1000-inpatient bed capacity. It provides medical services to Saudi citizens from all over the country. The anticoagulant clinic offers follow-up services to all of our discharged patients who are receiving anticoagulants. The study lasted for a period of 6 weeks. All patients with an age ≥16 years who were discharged from hospital on warfarin, and were taking the drug and attending the outpatient anticoagulant clinic at the King Khalid University Hospital for ≥6 months were asked to partake in the study during a regular clinic visit. The consent was taken from all participants prior to starting the questionnaire. Researchers administered the questionnaire face to face with the patients and recorded the answers.

To obtain an INR which reflected the warfarin dose and to obtain complete data, the following patients were excluded from the study; if the patients had a disruption in warfarin therapy for ≥5 days during the study period; if they were hospitalized for any reason during the study period; and if they did not have four consecutive INR readings or had an incomplete questionnaire.

Adherence was assessed using the Arabic version of the Morisky Medication Adherence Scale (MMAS-8). The MMAS-8 is a self-reported questionnaire that has been frequently used because of its low levels in both cost and time expenditure. Although earlier studies showed that the self-report method was underestimating non-adherence when compared with pill counts or biological assays, later studies suggest that the self-report method provides a reasonably accurate estimate of adherence. The MMAS-8 has been validated in many studies in patients with diabetes mellitus (Lee et al., 2013), hypertension (Korb-Savoldelli et al., 2012), and those taking warfarin (Wang et al., 2012). An 8-item self-report scale measured medication-taking behavior (Morisky et al., 2008, 1986). Items 1–7 were recorded as ‘yes/no’ dichotomous responses (scored 0/1) and item 8 was recorded using a 5-point Likert scale (never/rarely scored 1, other responses scored 0; Table 4). Thus, the total score of the 8-item scale ranges from 0 to 8 and a total score of 8 was considered to represent high adherence and scores ≤7 were considered as low-adherence.

The translation to Arabic language for MMAS-8 was done by using “The Eight Steps Translation Process” that combined the recommendations of WHO (World Health Organization, 2007) and (Brislin, 1986) after placing “warfarin” in each item. To assess the anticoagulation control, the most recent consecutive four INR readings, at an average of 4 weeks apart were obtained from the hospital central laboratory electronic data system for each patient. Anticoagulation control was defined as INR between 2 ≥3.0 for all indications except for mitral valve replacement (2.5–3.5): Good INR control was defined as percent Time INR in Therapeutic Range (TTR) ≥75% during study period using the Rosendaal method (Rosendaal et al., 1993). Previous studies had considered TTR ≥75% as good INR control (Davis et al., 2005; Wang et al., 2013).

Sensitivity and specificity of the MMAS-8 were calculated to determine the usefulness of the scale in identifying patients with poor anticoagulation control. Internal consistency of the MMAS-8 was measured using Cronbach’s $\alpha$ with correlated item-total correlations.

The questionnaire was validated in a crossover pilot study conducted on 25 patients who were currently using warfarin from the same clinic. It was done on two separate occasions, and two weeks apart to avoid duplication of their first responses and the Cronbach’s $\alpha$ was calculated. The value was 0.76 with moderate reliability.

Descriptive statistics (means, standard deviation, median, range, counts and percentages) were used to describe the quantitative and categorical study variables. Pearson’s Chi-square tests and Fisher’s exact test were used to detect if there were any associations between demographic characteristics, adherence and anticoagulation control. Univariate odds ratios were calculated between the categorical study and outcome variables were calculated to measure the strength of association. Multivariate binary logistic regression analysis was used to find out the independent associated variables among demographic background relating to adherence and anticoagulation control. A $p$-value of <0.05 and 95% confidence intervals were used to report the statistical significance and precision.
of the estimates. Statistical analyses were conducted using the Statistical Package for Social Science (SPSS) software (SPSS Inc., Chicago, IL), version 18.0.

3. Results

Three hundred and ten patients were invited to interview at the outpatient anticoagulation clinic during study period. Two hundred and eleven patients accepted the interview, which gave a response rate of 68.1%. Nineteen patients were excluded from the analysis due to the following reasons: incomplete INR results (4); disruption in warfarin therapy (6); and a substantial number of survey questions were not disclosed (9). The demographic and other patient characteristics of the 192 subjects are summarized in relation to their adherence and level of anticoagulation control in Table 1.

The mean age of the study population was 53.8 years (SD ± 15.2). Among the 192 participants, 129 (67.2%) were female, 136 (71.2%) were aged 50 and above, 163 (86.7%) were non-smokers and 145 (75.7%) were married. Sixty participants (31.4%) had not had any formal education and only 40 (20.9%) had a university diploma. Seventy-six participants (39.8%) participants stated they had a job, and the remainders were unemployed or dependents (Table 1).

3.1. Adherence to warfarin treatment

The mean score for the medication adherence scale was 6.78 (SD ± 1.22), and median score was 7 (range 1–8). The mean ages were similar in the high and low-adherence groups, 53.6 SD ± 15.2, and 52.3 SD ± 14.6, respectively. Eighty-nine patients (46.4%) reported to having high adherence (scored 8) and 103 (53.7%) had low adherence to warfarin therapy.

Univariate tests showed that when the age is less than 50 years (OR 2.56, 95% CI 1.16–5.56) it is associated significantly with low adherence (score ≤ 7) to warfarin therapy (Table 1). Multivariate logistic regression analysis showed that when the age was less than 50 (OR 2.67, 95% CI 1.29–5.52) and the education status was no formal education (OR 2.63, 95% CI 1.01–6.93), it was independently associated with low adherence (score ≤ 7) to warfarin therapy.

3.2. Anticoagulation control

The mean ± SD INR values obtained for four readings were as follows: INR 1st reading 2.57, SD ± 0.87, range 0.93–8.03; INR 2nd reading 2.56, SD ± 0.79, range 1.05–6.78; INR 3rd reading 2.67, SD ± 0.86, range 0.92–6.74, and 4th reading 2.73, SD ± 0.77, range 1.16–6.71. The mean INR follow-up days were 121 SD ± 39. Only 68 (35.4%) of the participants had good anticoagulation control (TTR > 75%) during the study period. Of the 124 participants with poor anticoagulation control (TTR < 75%), 51 (41.1%) patients had INR values below the therapeutic range, and 73 (58.9%) had INR values above therapeutic range. Univariate tests showed the occupational status as unemployed (OR 2.56, 95% CI 1.16–5.56, p = 0.03), and females (OR 1.97, 95% CI 1.06–3.67, p = 0.02) were significantly associated with poor INR control (Table 2). Multivariate logistic regression analysis

| Table 1 | Association between demographic factors and adherence to warfarin treatment. |
|----------|-------------------------------------------------------------------------|
| Characteristics | Total | Low adherence combined (n, %) | High adherence (n, %) | OR (95% CI) | p value |
| Age | | | | | |
| < 50 years | 55 | 37 (67.3) | 18 (32.7) | 2.18 (1.13, 4.20) | 0.02 |
| ≥ 50 years | 136 | 66 (48.5) | 70 (51.5) | 1.0 | – |
| Gender | | | | | |
| Male | 63 | 31 (49.2) | 32 (50.8) | 1.0 | – |
| Female | 129 | 72 (55.8) | 57 (44.2) | 1.30 (0.71, 2.38) | 0.39 |
| Marital status | | | | | |
| Married | 145 | 76 (52.4) | 69 (47.6) | 1.0 | – |
| Others (unmarried, divorced/widow) | 47 | 27 (57.4) | 20 (42.6) | 1.23 (0.63, 2.38) | 0.55 |
| Education | | | | | |
| No formal education | 60 | 41 (68.3) | 19 (31.7) | 1.59 (0.69, 3.66) | 0.27 |
| Primary/middle school | 91 | 39 (42.9) | 52 (57.1) | 0.55 (0.26, 1.18) | 0.12 |
| Diploma/university | 40 | 23 (57.5) | 17 (42.5) | 1.0 | – |
| Occupational status | | | | | |
| Employed | 76 | 38 (50.0) | 38 (50.0) | 1.0 | – |
| Unemployed | 50 | 29 (58.0) | 21 (42.0) | 1.38 (0.67, 2.83) | 0.38 |
| Dependent | 65 | 35 (53.8) | 30 (46.2) | 1.17 (0.60, 2.26) | 0.65 |
| Smoking status | | | | | |
| Previous or current smoker | 25 | 15 (60.0) | 10 (40.0) | 1.13 (0.56, 3.09) | 0.54 |
| Non smoker | 163 | 87 (53.4) | 76 (46.6) | 1.0 | – |

Independent variable associated with adherence to warfarin treatment (by multivariate logistic regression analysis)

| Variables | Adjusted odd ratio | p value |
|-----------|--------------------|---------|
| Age < 50 | 2.67 (1.29, 5.52) | 0.008 |
| Education (no formal education) | 2.63 (1.01, 6.93) | 0.049 |
also showed females (OR 2.31, 95% CI 1.10–4.92) and occupational status as unemployed (OR 2.71, 95% CI 1.12–6.61) were independently associated with poor INR control.

3.3. Association between adherence to warfarin treatment and anticoagulation control

No association was found between the MMAS category (high and low adherence) and INR control groups ($X^2 = 2.12, p = 0.347$). Eighty-nine patients (46.4%) had high adherence (score = 8), 34 (38.2%) had good INR control versus 103 (53.6%) patients who had low adherence (score ≤ 7) and 34 (33.0%) had good INR control (Table 3).

The sensitivity and specificity for MMAS-8 were determined using INR control as a gold standard. The MMAS-8 had a sensitivity of 55.7% (range 46.6%–64.7%), specificity of 50.0% (37.6%–62.4%), positive predictive value of 66.9% (47.0%–75.9%) and negative predictive value of 37.8% (range 28.1%–49.1%). The sensitivity means that 69 (55.6%) of 124 patients who had poor INR control had low and medium warfarin adherence while the specificity indicates that 34 (50%) of 68 patients with good INR control had high adherence to their medication. The positive predictive value indicates that 69 (55.6%) of 103 patients with low and medium adherence had poor control whereas 55 (37.8%) of 89 patients with high adherence had good INR control.

The analysis of response allocation to each of the questions of the Arabic version of MMAS-8 is shown in Table 4. All the participants were able to answer >75% of the MMAS-8 questions correctly. Cronbach’s $\alpha$ for internal consistency was 0.650 for the MMAS-8. The item-total correlation coefficients were greater than 0.3 and ranged from 0.305 to 0.685 (Table 4).

4. Discussion

This is the first study to explore the patient adherence to warfarin treatment using the MMAS-8 Arabic translated version and further investigates the association between therapy
adherence and anticoagulation control (INR) in the Saudi population. The mean adherence score of the study was 6.78 ± 1.22, it had a high-adherence rate of 46.4% and a good INR control rate of 35.4%. The findings are consistent with a study recently conducted in Singapore to investigate the adherence of warfarin treatment in 174 patients using Chinese and English versions of MMAS-8. The mean adherence score for the MMAS-8 was 7.0 ± 1.1, a high-adherence rate (score = 8) of 34.5%, and a good INR control (≥80%) of 39.1% (Wang et al., 2013). Also, a study conducted in 2013 in Saudi Arabia using Arabic versions of MMAS-8 to examine adherence to long-term medications in 408 patients with chronic medical conditions. Their results showed 56.9% of participants had good medication adherence (score = 8) that is similar to that observed in the current study (Alhewiti, 2014).

Furthermore, studies performed in patients of other ethnic groups taking warfarin have reported approximately 80–90% adherence using methods other than MMAS-8 to assess adherence (Orensky and Holdford, 2005; Parker et al., 2007). On the contrary, a Korean study reported less than 30% of their studied group could adhere to prescribed medications. They did not use Morisky scale to assess the warfarin adherence. The medication adherence was characterized by how well patients were following warfarin instruction (frequency, dosage, time, and precautions) that had been given to them (Kim et al., 2011).

The current study did not find high adherence (46.3%) to warfarin therapy that contributed to good INR control (35.4%) in patients attending the outpatient clinic. The association between warfarin therapy adherence and anticoagulation control in the literature varies. Davis et al. had noticed a significant association between medication adherence and good anticoagulation control by using Morisky scale. Fourteen percent of their patients achieved good INR control (≥70%) and 50% of patients had adequate adherence to warfarin treatment. However, the study sample size was small with only 52 participants, and the TTR% was calculated on an INR result obtained within 60 days prior to survey completion. It was half of the current study follow-up of 120 days (Davis et al., 2005). A study from Singapore by Wang et al. in 2012 also reported a significant association between anticoagulation control and warfarin adherence. The study consisted of 151 patients, using English and Chinese versions of MMAS-8 to assess the adherence. The mean score for adherence was 7.0; one-third of patients had the highest adherence (score = 8) and showed a significant association between a high-adherence score and TTR ≤ 80% (p = 0.01). However the study did not mention how TTR and the TTR percent were calculated on an INR result obtained only within 14 days prior to survey completion. This was much shorter than our study follow-up of 120 days (Wang et al., 2012). On the contrary, Kim et al.’s cross-sectional survey could not associate between adherence and anticoagulation control. However, the study did not use the Morisky scale to assess the medication adherence. The adherence was assessed by how well patients followed warfarin instruction given to them (Kim et al., 2011).

The MMAS-8 Arabic translated version of the study had moderate reliability in patients taking warfarin with Cronbach’s α of 0.65 which is greater than 0.5, and is an acceptable value (Nunnally and Bernstein, 1994; Streiner and Norman, 2008). The MMAS-8 was validated in different languages in patients with hypertension, diabetes mellitus, and those taking warfarin and though the results were varied (Cronbach’s α 0.53–0.84) they were considered as moderately reliable (Korb-Savoldelli et al., 2012; Sakthong et al., 2009; Wang et al., 2012). Corrected item-total correlation coefficient

| Table 4 | Responses from the eight-item Morisky medication adherence scale administered to patients who were on warfarin. |
|----------------|---------------------------------------------------------------------------------------------------------------|
| **Items** | **Patient responses** | **Corrected item-total correlation** | **Cronbach’s alpha if item deleted** |
| 1. Do you sometimes forget to take warfarin? (n = 192) | No 144 (75.0) | Yes 48 (25.0) | 0.685 | 0.507 |
| 2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your warfarin? (n = 192) | No 162 (84.4) | Yes 30 (15.6) | 0.515 | 0.566 |
| 3. Have you ever cut back or stopped taking warfarin without telling your doctor because you felt worse when you took it? (n = 192) | No 176 (91.6) | Yes 16 (8.3) | 0.409 | 0.597 |
| 4. When you travel or leave home, do you sometimes forget to bring along your warfarin? (n = 192) | No 171 (89.1) | Yes 21 (10.9) | 0.305 | 0.612 |
| 5. Did you take all your warfarin yesterday? (n = 192) | No 40 (20.8) | Yes 152 (79.2) | 0.300 | 0.613 |
| 6. When you feel like your symptoms are under control, do you sometimes stop taking your warfarin? (n = 192) | No 186 (96.9) | Yes 6 (3.1) | 0.451 | 0.609 |
| 7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your anticoagulation therapy? (n = 191) | No 157 (82.2) | Yes 34 (17.8) | 0.274 | 0.616 |
| **Item 8** | **Patient responses** | **Internal reliability** |
| 8. How often do you have difficulty remembering to take your warfarin? (n = 187) | Never 153 (81.8) | Once 8 (4.3) | 0.511 | 0.604 |
| | Sometimes 7 (3.7) | Usually 19 (10.2) | | |
value was > 0.3, indicating that the Arabic version of MMAS-8 had good homogeneity. The MMAS-8 had poor sensitivity and specificity (55.7%, 50.0%) in the current study. Although previous studies suggested that the self-report method (MMAS-8) may provide cost effective and reasonably accurate estimate of adherence, this method needs to compare with other well-known used tools such as prescription refills, pill counts or direct observation of therapy in the Middle East countries to reach an appropriate conclusion. Wang et al reported the MMAS-8 in patients taking warfarin had sensitivity and specificity of 73.0% and 35.6% (Wang et al., 2012). The study did not mention the method of calculating the TTR percent for INR. The INR record obtained for the past two weeks prior to survey administration was used to define percent TTR ≥ 80%.

The study had following limitations; its small sample size; the cross-sectional methodology; and a lack of fully validated instruments. Respondents in this study were recruited from an outpatient anticoagulant clinic therefore the results cannot be generalized to all patients.

5. Conclusion

The current level of adherence to warfarin therapy in our patients is reasonable. No association was found between adherence to warfarin therapy and anticoagulation control. The MMAS-8 has moderate reliability in patients taking warfarin, but the psychometric properties of the scale need to be investigated in other clinical settings. Additional studies that can recognize factors predicting favorable anticoagulation control are also required.

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