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Pharmacist-led interventions might improve quality of life among older adult patients receiving warfarin treatment in rural areas: results from a randomized controlled trial

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Abstract

Background: Available literature supports the role of a pharmacist in the management of patients on warfarin therapy. However, randomized controlled trials on the influence of pharmacists' interventions on the quality of life (QoL) in elderly patients on warfarin are missing. The aim of this study was to investigate the effect of pharmacists' interventions on QoL of older adult patients receiving warfarin therapy in rural areas. The study aimed also to explore factors influencing QoL in these patients.

Methods: We conducted a prospective randomized trial in a community pharmacy setting in a rural area. Eligible patients were randomized into intervention and control groups. Repeated education and a follow up plan were provided to the participants in the intervention group, and, if needed, pharmacist intervened to optimize warfarin therapy in collaboration with GP. QoL was measured using the DASS (Duke Anticoagulation Satisfaction Scale) questionnaire in both groups after 6 months.

Results: In total, 131 participants finished the study (median age 73 years; 51.1% men). Participants in the intervention group scored significantly lower in all 3 domains of the DASS questionnaire at 6 months, namely limitations, hassles and burden, and psychological impact, as well as in overall scores (median score 86.5 and 66.0 in control and intervention group, respectively; $p<0.001$), indicating higher QoL in the intervention group. Adverse drug reactions (ADRs) and pharmacist's intervention were predictive of QoL ($r^2 =65.5\%$, $P<0.001$). Experience of ADRs was the strongest negative predictor of QoL ($P<0.001$).

Conclusions: The study demonstrated that pharmacist's intervention had positive impact on the QoL among older adult patients in rural areas. ADRs and pharmacist's intervention were identified as predictive factors for QoL, whereby experience of ADRs was the strongest negative predictor. These results suggest that older adult patients receiving warfarin in rural areas could benefit from a community pharmacist intervention.

Background

Warfarin remains a widely prescribed anticoagulant for indications such as atrial fibrillation, cardiac valve replacement, deep vein thrombosis, and pulmonary embolism, although it is being gradually replaced by direct oral anticoagulants (DOACs). Nevertheless, warfarin's lower cost compared to DOACs, combined with its established efficacy and safety profile, make warfarin the most often used oral anticoagulant. Its popularity notwithstanding, warfarin therapy is complicated by several factors, such as narrow therapeutic index, risk of interactions with other drugs and food, and need for rigorous laboratory monitoring, among others. These limitations of warfarin use have been reported to impact on the quality of life (QoL) of its users [1].

Concurrently, assessment of pharmacists' interventions aimed at improving QoL in older adult patients has provided mixed findings, suggesting further research is needed [2, 3]. Moreover, a review Clarksmith et al. concluded that there is insufficient evidence to draw definitive conclusions regarding the impact of educational or behavioral interventions on time in therapeutic range (TTR) among patients with atrial

fibrillation receiving oral anticoagulation therapy. Furthermore, the same authors have suggested that it is important to explore the psychological implications for patients suffering from this long-term chronic condition [4].

Studies on psychological implications and QoL in patients taking warfarin imply that QoL in these patients is decreased [5, 6]. Therefore, finding the interventions that could improve QoL of patients taking warfarin would be of great interest. Following a literature review, we conclude that randomized controlled trials on the influence of pharmacists' interventions on the QoL in patients on warfarin are scarce and to the best of our knowledge no study has been done in primary care setting.

We have previously performed a randomized controlled trial to investigate the influence of the community pharmacist's intervention on the efficacy and safety of warfarin use, showing that pharmacist's interventions significantly improved TTR [7], and reduced the incidence of adverse drug reactions (ADR) among older adult patients living in rural areas [8]. The present work reports on the analysis of secondary outcome, which was the effect of pharmacists' interventions on the QoL among older adult patients taking warfarin while living in rural areas. An additional aim of the present study was to explore factors influencing QoL among warfarin patients. Herein, we present preliminary evidence that pharmacists can improve patients' quality of life through interventions in community pharmacy.

Methods

Study design, location of study and sample selection

The present study was retrospectively registered at Clinicaltrials.gov under the number NCT03212898, and its protocol complied with the CONSORT statement. The study was designed as a randomized controlled trial conducted at a single community pharmacy in a rural region of Croatia (Donji Miholjac). Using consecutive sampling, patients on warfarin therapy who came to the community pharmacy were recruited. The inclusion criteria were: 1) aged 65 years or older; 2) rural place of residence; 3) taking warfarin for at least 3 months before study enrollment with the expected duration of therapy of at least another 6 months. Patients were excluded if they were prescribed a drug that interacts with warfarin with an x degree of clinical significance, based on the Lexi®-interaction database. The patients were randomized into an intervention and control group, using a computer-based randomization program (www.randomization.com). Details of the study design and protocol are available elsewhere [7, 8].

Written informed consent was obtained from each patient. Ethical approval (number 251-62-03-15-28) was obtained from the Ethical Committee of the Faculty of Pharmacy and Biochemistry, University of Zagreb.

The intervention group was repeatedly educated on all aspects of warfarin therapy during monthly visits to the pharmacy and provided with a follow-up plan and a pillbox. Warfarin dose adaptation or therapy change to avoid drug interactions were done in collaboration with general practitioners (GPs). The control

group received standard care from their GPs without pharmacist-delivered education on warfarin therapy or other interventions. The follow-up period was 6 months.

Data collection

At the initial visit, clinical pharmacist interviewed each patient and collected data on their sociodemographic and clinical characteristics, including medication history. Data on comorbidities, indication for pharmacotherapy, and INR (international normalized ratio) were subsequently collected from patients' medical records provided by their GPs and from the pharmacy database. During the monthly follow-up visits, a clinical pharmacist performed medication therapy review and examined laboratory and physical examination results provided in the medical records. TTR was calculated by the Rosendaal method [9]. The patients were asked about the experience of ADRs related to warfarin and consumption of food rich with vitamin K (including kale, collard, spinach, parsley, endive, and cabbage, among others) in order to avoid drug-food interactions. Treatment adherence was measured with the number of pills left in the pillbox or pill package at the time of the visit. All study participant completed DASS (Duke Anticoagulation Satisfaction Scale) [10] questionnaire at the end of the study period (after 6 months).

Measurement of health-related quality of life

We used the DASS questionnaire to measure QoL of patients taking anticoagulant therapy. The DASS is a tool developed to evaluate the QoL of patients taking oral anticoagulants. The questionnaire has 25 items and considers 3 domains: 1) limitations; 2) hassles and burden, and 3) psychological impact. Each item is assessed using a 7-point Likert scale (ranging from 1 for "not at all" to 7 for "very much"). The overall score varies from 25 to 175, whereby the lower the scores, the higher the QoL. Items negatively worded were reverse-coded during data entry (specifically, items: 19, 21, 22, 23, 25, and 27). A Croatian version of this tool was developed for the purpose of this study and the adaptation process ensured its conceptual equivalence to the original English version. The adaptation process involved linguistic validation and cultural adaptation. None of the questions was omitted or altered. The DASS questionnaire was completed on paper during a face-to-face interview with the pharmacist. Study participant in the control and intervention groups completed the questionnaire at the end of the study (after 6 months).

Statistical analysis

Normality of variable distribution was assessed by the Kolmogorov-Smirnov test. Data were presented as percentages (%) for categorical variables and as median and interquartile range (IQR) for non-normally distributed numerical variables. Mann-Whitney U-test was used to test the differences in baseline characteristics expressed as interval variables between the intervention and control groups. Chi-square test was used for comparisons between proportions. A multiple regression model was used to evaluate the contribution of each independent variable (TTR, number of comorbidities, age, gender, ADR appearance, adherence rate, educational level, and pharmacists' intervention) to the change in the overall

DASS score. Statistical significance was set as a p-value < 0.05 (2-sided). Statistical analysis was performed in IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Results

Patients' baseline characteristics

Of the 160 patients meeting the inclusion criteria, 140 agreed to participate in the study and were randomized to the intervention (n=70) and control group (n=70). Nine patients dropped out before the end of the study (5 in intervention and 4 in the control group), leaving the final sample of 131 patients to be included in the analysis.

The median age was 73 (IQR 70–80) years, with 71.8% of the patients in the age range between 65 and 80 years, and 28.2% of the patients ≥80 years old. Overall, 51.1% of the participants were men, with the majority having achieved elementary school education only (67.2%). Nearly half of the participants were married (49.6%). The most common indication for warfarin therapy was atrial fibrillation (74.1%), while median number of comorbidities was 4 (IQR 4–5) and median number of drugs in the therapy was 6 (IQR 5–7). There were no significant differences between the intervention and control group on clinical or demographic characteristics (Table 1).

Outcome measures at 6 months

During the follow up period TTR, adherence, and ADRs were monitored in both groups (Table 2). Details of these outcomes have been reported previously [7,8]. There were significant differences between the groups on all 3 outcomes (p<0.001); overall, the results were more favorable in the intervention group.

Patients' satisfaction with warfarin therapy at 6 months

The DASS questionnaire scores for both groups are presented in Table 3, divided into the overall and domain-based scores. There were statistically significant differences between the groups in all 3 domains and the overall score. Participants in the intervention group scored lower across all domains, indicating higher warfarin-related satisfaction and QoL compared to the control group.

Predictors of patients' satisfaction with warfarin therapy

Out of 9 variables entered into the regression model, only ADRs and pharmacist's intervention were identified as predictive factors (r^2=65.5%, P<0.001) (Table 4). Experience of ADRs was the strongest predictor of higher DASS scores (lower satisfaction), accounting for 52.7% of variance of the overall model. Experiencing ADRs and not being exposed to the pharmacist's intervention were positive predictors of lower satisfaction with warfarin therapy after the 6-month period.

Discussion

To the best of our knowledge, this is the first randomized controlled study exploring the effect of a community pharmacist's intervention on the QoL of older adult patients receiving warfarin therapy in rural areas. In the present study, a pharmacist's intervention had a positive impact on the QoL of the patients on warfarin therapy.

As this is the first study of its kind, there are no previous studies that would allow direct comparison of findings. As such, we discuss our findings in the context of previous studies that involved a different population or setting. For example, a meta-analysis performed by Mohammed et al., which included 48 studies, found that pharmaceutical care interventions can significantly improve at least one domain of health-related QoL [11]. However, only one of the included studies involved patients on anticoagulants. This study was performed in tertiary care setting and compared pharmacist-led warfarin self-management program with standard care at an anticoagulation clinic, showing benefits of the pharmacist-led program [12].

Overall, at the end of the study, we observed improved QoL and satisfaction in the intervention group across all 3 domains of the questionnaire. Our results are consistent with data published by Elewa et al. [13] In their nonrandomized study, the overall QoL score of patients attending an anticoagulation clinic run by pharmacists in Qatar was 63, which is comparable to the score achieved in the intervention group in our study. It should be noted that the DASS questionnaire used in their study was modified in a cultural adaptation process, and one question was left out (regarding consumption of alcoholic beverage), bringing the questionnaire to 24 items.

In an observational study, Hasan et al. found that the QoL of patients taking warfarin over 1 year declined significantly [5], which might not be surprising given the side effects, periodic monitoring that entails discomfort for the patient, and other therapy-associated limitations. Furthermore, Matchar et al. have shown that the QoL increases when the patient is less dependent on a visit to the doctor or laboratory and can monitor the INR at home, using a portable device (known as point-of-care testing [POCT]) [14]. The same authors have also emphasized that such testing does not affect clinical outcomes or mortality. Similarly, Sølvik et al. [15] concluded that QoL was improved in patients who self-control INR and self-titrate warfarin doses. According to these authors, patients who switch from conventional care to the self-care model after 2 years have a significantly higher QoL, probably because they are less dependent on going to the doctor. In contrast, Carris et al. found that anticoagulation satisfaction following extended interval monitoring, as measured by the DASS questionnaire, did not change or may have marginally worsened after an extended interval follow up, which was contrary to expectations [16]. The authors suggest that less frequent feedback and patient-provider interaction might have resulted in reduced patient perception of benefit from anticoagulation and reduced self-management activities [16]. We agree with the last observation and believe that intervention group in our study benefited from more frequent patient-provider interaction.

Our secondary aim was to establish factors predictive of QoL. Among 9 analyzed variables, only pharmacist intervention and experience of ADRs predicted QoL. Experience of the ADRs was identified as

the strongest predictor for lower QoL. Hemorrhagic events negatively influenced QoL in a previous study by Lancaster et al. [17]. In contrast, they did not influence QoL in a study by Casais et al. [18]. Although other studies have reported different findings on the association between ADRs and QoL, based on our results, we recommend focusing on the management of ADRs to increase QoL of patients on warfarin. As most of the ADRs recorded in our sample were not serious (i.e. bruising), we believe that counseling patients on minor bleeding signs would increase patients' overall satisfaction with warfarin therapy.

Concurrently, other studies have identified socio-demographic factors that influence QoL in patients on warfarin [5, 19]. Although Hasan et al. have shown that men score higher [5], in our study this effect has not been confirmed. Neither years played a role unlike other studies [5, 19], probably because our sample was more homogeneous, that is, it included only elderly people. Almeida et al. have shown that, in a cohort of Brazilian patients who were 67 years old, QoL was influenced by experience of side effects, age, comorbidities, drug interactions, level of education, and duration of treatment [19].

We believe that our results significantly contribute to the QoL and pharmaceutical care research. Measuring humanistic outcomes in the form of health-related QoL, in addition to clinical and economic outcomes, provides a comprehensive picture of the impact of a healthcare intervention [20]. Improving or maintaining patients' QoL is a fundamental goal of pharmaceutical care services [11]. Well-known definitions of pharmaceutical care by Hepler and Strand, and later by Cipole et al., stress the importance of QoL in pharmaceutical care stating that pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve and maintain a patient's QoL [21, 22].

Depending on a country's development, rural areas might face difficulties in providing quality healthcare and clinical pharmacist services, as documented by Patterson et al. in a sample of more than 3 million patients [23]. Warfarin patients require frequent visits to the laboratory and doctor, which can be difficult in a rural context. Even in well-developed countries and health systems, such as the United States, in urban areas, patients with atrial fibrillation received warfarin more often than did patients in rural areas, despite comparable risk of stroke [24]. A large study by Rose et al., involving 56,490 older patients, showed that there was a loss to follow-up for such patients and that they did not engage with regular laboratory monitoring, while the risk of loss to follow-up was associated with race, poverty, dementia, depression, and remoteness [25]. The present study highlights that community pharmacists are an important factor to overcoming barriers to care experienced by some warfarin patients.

These observations have important clinical implications for rural regions and are especially applicable in countries where pharmacists-managed anticoagulation monitoring services are not common. Patients living in socially deprived regions with restricted access to healthcare facilities and who need support with their warfarin therapy could benefit from a community pharmacist-managed service.

Limitations

Since the QoL instrument was not applied before and after the pharmacists' intervention, we were not able to observe the magnitude or the direction of change in the QoL. Nevertheless, the randomized controlled design of our study allowed observing a positive effect in the intervention group. This aspect notwithstanding, our results are applicable to a specific population and cannot be generalized. The isolation of these patients, low level of education, and increased availability of healthcare could have created a stronger positive impact of the pharmacy-based interventions in the study patients.

Conclusion

This study demonstrated that pharmacy interventions conducted at a community pharmacy level might positively affect the QoL of older adult patients on warfarin therapy, living in rural areas. In rural areas, community pharmacists are the most assessable healthcare professionals and could play an important role in patient care. Finally, the results of this study indicate the importance of focusing on the ADRs related to warfarin therapy to improve patients' QoL.

Abbreviations

DOAC
direct oral anticoagulant drugs
QoL
quality of life
TTR
time in therapeutic range
GP
general practitioners
DASS
Duke anticoagulation satisfaction scale
IQR
interquartile range
INR
international normalized ratio
ADR
adverse drug reaction

Declarations

Ethical approval and consent to participate

Ethical approval (number 251-62-03-15-28) was obtained from the Ethical Committee of the Faculty of Pharmacy and Biochemistry, University of Zagreb. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All the authors declare that they have no competing interests.

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The authors have no funding sources to disclose.

Author contributions

SF has the main role in the conceptualisation of the study. All authors contributed to the study conception and design. Material preparation and data collection were performed by SF. All the analysis were performed by MOH and ML. The first draft of the manuscript was written by MOH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Baseline sociodemographic and clinical characteristics of the study participants

Variable	All participants (n=131)	Control group (n=66)	Intervention group (n=65)	P-value
Age (years)	73 (70–80)	74.5 (71–81)	72 (68–79)	0.053
Gender (male)	67 (51.1%)	34 (51.5%)	33 (50.8%)	0.932
Indication:				
Atrial fibrillation	97 (74,1)	47 (71.2%)	50 (76.9%)	
Phlebothrombosis	12 (9.2%)	6 (9.1%)	6 (9.2%)	0.456
Other	22 (16.8 %)	13 (19.7%)	9 (13.8%)	
Number of comorbidities	4 (4–5)	4 (4–5)	5 (3–5)	0.408
Number of drugs in therapy	6 (5–7)	6 (5–7)	6 (5–8)	0.187
Education				
No formal education or elementary school	88 (67.2%)	47 (71.2%)	41 (63.1%)	0.260
High school	37 (28.2%)	15 (22.7%)	22 (33.8%)	
College/ University	6 (4.5%)	4 (6.1%)	2 (3.1%)	

Data presented as count (n [%]) or median (interquartile range).

P-values presented correspond to the results of Mann-Whitney U test for numerical data or chi-squared test for categorical variables.

Table 2. Adverse drug reactions incidence, patients' adherence to warfarin therapy and estimated TTR at the end of the follow-up period.

Variable	Control group	Intervention group	P-value
Time in therapeutic range	31.2 (0–50.2)	93 (71.7–100)	<0.001*
ADRs n (%)	56 (85%)	19 (29%)	<0.001**
Bruising (n, %)	46 (70%)	19 (29%)	<0.001**
Minor bleeding[1] (n, %)	7(10%)	0	0.006**
Major bleeding[2] (n, %)	3 (5%)	0	0.244**
Adherence	69.0 (64.3–72.5)	80.2 (75.9–87)	<0.001*

Falamić et al. Int J Clin Pharm. 2018;40:1078–1085. Falamić et al. Int J Clin Pharm. 2019;41:1166–1173.
[1] bleeding from nose or gums, [2] bleeding requiring medical intervention
* P-value corresponds to the results of Mann-Whitney U test
** P-values correspond to the results of a chi-squared test
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Table 3. Duke Anticoagulation Satisfaction Scale[10] scores at the end of the study period (after 6 months)

DASS domain	Control	Intervention	P-value
Limitations	23.0 (21.0–26.0)	17.0 (16.0–18.8)	<0.001
Hassles and burden	23.0 (19.0–25.0)	16.0 (15.0–18.0)	<0.001
Psychological impacts	41.0 (35.0–43.0)	33.0 (32.0–35.0)	<0.001
Overall DASS	86.5 (77.0–94.0)	66.0 (63.0–69.0)	<0.001

* P-value corresponds to the results of Mann-Whitney U test

Table 4. Predictive variables for patients' satisfaction with warfarin therapy after 6 months resulting from multiple regression analysis

Variable	Unstandardised (B) coefficient	Standard error	Standardised (beta) coefficient	P-value
Time in therapeutic range	0.021	0.042	0.049	0.619
Number of comorbidities	-0.108	0.709	-0.008	0.879
Age	0.253	0.161	0.108	0.119
Gender (female)	2.086	1.873	0.070	0.267
Education level (higher)	-1.408	1.733	-0.054	0.418
Adherence	-0.073	0.108	-0.051	0.500
Pharmacist's intervention	-9.513	2.878	-0.317	0.001*
ADR	11.435	1.587	0.527	<0.001*
Marital status (not married)	0.380	2.183	0.013	0.862

R^2=65.5%; adjusted R^2=63.0%, p<0.001
*Statistically significant

Supplementary Files

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- CONSORT2010Checklist.doc