Characterization and evaluation of patients anticoagulated with warfarin in relation to the complexity of pharmacotherapy

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Abstract

Diagnosis and treatment of sustained arrhythmias are part of the clinical routine, with one of the most frequent arrhythmias being Atrial Fibrillation (AF). To prevent thromboembolic events in patients with AF, oral anticoagulation is recommended, particularly warfarin. Despite its importance, this medication has a narrow therapeutic range, which means that small changes in treatment generate a risk of thrombotic or hemorrhagic events. Among these changes, adherence to other medications in use, changes in the use of these medications by prescribers and self-medication stand out. There are several interactions between warfarin and other medications for continuous use, with the belief that the complexity of the prescription may interfere with the clinical outcomes of anticoagulant therapy. The objective of the study was to characterize patients followed in an anticoagulation outpatient clinic in relation to the Pharmacotherapy Complexity Index. To identify the complexity of pharmacotherapy, prescriptions for other medications in use, prescribed by primary health care doctors, were considered. The Medication Regimen Complexity Index (MRCI) instrument was used. Complexity, understood as the form of administration, dosage and pharmaceutical form, factors that interfere with adherence to anticoagulant therapy, was subdivided into three complexity levels: low, moderate and high, as indicated in the literature. The complexity analysis was carried out by two researchers independently, considering the criteria as per MRCI guidance. This is a descriptive study carried out in two anticoagulation clinics, located in Minas Gerais. During the research, patients were monitored in two anticoagulation clinics in Brazil, using warfarin, and were invited to participate in a clinical trial between December 2018 and February 2019, and a selection was subsequently made for the present study. A total of 93 patients were included in the study, the average age was 63 years and the majority were female (68.8%). Atrial fibrillation was the most predominant OAC indication (92.5%). The average number of medications used was 7.0. The majority of patients with pharmacotherapy classified as high (38, 6.5%) and medium complexity (24, 80.7%) presented inadequate TTR. The present study identified that there is a predominance of patients with high complexity of pharmacotherapy, which may indicate the need for additional care in relation to anticoagulant treatment. Therefore, in cases of patients with inadequate control of oral anticoagulation, it is recommended that aspects of the complexity of pharmacotherapy be incorporated into the educational approach.

Keywords: Warfarin. Health Literacy. Anticoagulants. Cooperation and Adherence to Treatment. Polypharmacy.

INTRODUCTION

Diagnosis and treatment of sustained arrhythmias are part of the clinical routine, one of the most frequent arrhythmias being Atrial Fibrillation (AF)1. This health problem arises from
a derangement of coronary pacemakers, triggering loss of atrial contraction and consequent emergence of thromboembolic events\(^1\).

To prevent thromboembolic events in patients with AF, oral anticoagulation is recommended, particularly warfarin\(^1\). This medication works by inhibiting coagulation factors II, VII, IX and X, which depend on vitamin K\(^2\).

Monitoring the effectiveness of warfarin occurs by measuring the International Normalised Ratio (INR), assessed by comparing the user’s prothrombin time in relation to the control, corrected according to the sensitivity index of the thromboplastin reagent used and provided by the manufacturer. INR can be altered by the interaction of warfarin with foods rich in vitamin K and various medications, making it a challenge in anticoagulant treatment\(^1\).

Treatment with warfarin requires patients’ understanding and participation in the care process, which can be impacted not only by the medications in use, but by the complexity of pharmacotherapy. This includes the form of administration, dosage and pharmaceutical form, as well as factors that interfere with adherence to anticoagulant therapy.

Although it is of great importance for clinical practice, the complexity of pharmacotherapy is little addressed in scientific studies, especially those related to oral anticoagulation. The present study aims to characterize the complexity of pharmacotherapy of patients treated in two anticoagulation clinics (AC) in Belo Horizonte, Minas Gerais (MG).

METHODS

This is a descriptive study carried out in two ACs, located in Minas Gerais. Data collection took place from December 2018 to February 2019. One of the ACs is located in a public university hospital (hospital 1), integrated into the SUS, and the other in an open-door teaching hospital, a reference in urgency and emergency (hospital 2).

In both ACs, patients are evaluated by a doctor or pharmacist after performing the INR exam. During the anamnesis, lifestyle, eating habits and medications in use are considered. If necessary, the warfarin dose adjustment and new test order are performed as recommended by institutional protocols. To calculate the TTR, the values of the INR exam carried out between January and March 2019 were considered, the period prior to the intervention of the clinical trial from which the present study was selected. An average of 5.9 INR exams were performed for each patient during this period, which were used to calculate the TTR.

The inclusion criteria were: age over 18 years, diagnosis of AF, use of warfarin for more than 60 days and attendance at one of the ACs under study between December 2018 and February 2019. The exclusion criteria were: presentation of less than two INR values in the period from July to December 2018.

Patients were approached to participate in the study in the CA by previously trained undergraduate pharmacy students. At this point, the objectives of data collection were presented, presentation of the Informed Consent Form (ICF) and, in case of agreement, request for its signature. To identify other medications and their use, all participants were asked to provide a copy of the prescription written by the doctor responsible for each patient at PHC.

To analyze the complexity of pharmacotherapy, the Medication Regimen Complexity Index (MRCI) instrument was used, validated in Brazilian Portuguese and with good psychometric properties. The MRCI is an instrument used to measure the complexity of an individual patient’s pharmacotherapy, divided into three sections: A, B and C. Section A corresponds to information on dosage forms; section B, information on dose frequencies; and section C corresponds to additional in-
formation, such as specific times and use with food, among others. Each section is scored based on the analysis of the patient's pharmacotherapy and the complexity index is obtained by adding the points (scores) of the three sections. Then, the points obtained in the three sessions were added together to obtain the Medication Regimen Complexity Index (MRCI)4.

For situations not included in the MRCI validation document, the following procedures were standardized for analysis: the use of acute medications was disregarded; the prescription of 1.5 tablets per day was standardized as “multiple doses”; in case of presentation of two different medical prescriptions in the last three months for the same patient, both were considered; in case of multiple prescriptions from the same doctor, the most recent one was considered.

Furthermore, it is worth noting that medications prescribed with “in the morning” and “on an empty stomach” mode of administration in the same sentence scored in two distinct categories in section C and medications prescribed with a longer interval were considered in section B.

Medical records were also consulted considering the variables: age, therapeutic target, sex, municipality of residence and indication of anticoagulation with warfarin and INR values, the latter being used to calculate the Therapeutic Time Range (TTR). The TTR indicates the quality of anticoagulation and is calculated using the Rosendaal method. This involves linear interpolation of INR values, expressed as a percentage, and requires a minimum number of two INR measurements to be made.

All variables were recorded in a Microsoft Excel spreadsheet and descriptive statistical analysis was performed. The present study is an excerpt from a clinical trial entitled “Evaluation of the implementation of an educational intervention for patients with ineffective oral anticoagulation with warfarin treated at a university hospital: controlled clinical trial”, registered in the Brazilian clinical trials registry (REBEC) under the code RBR-9cy6py e UTN U1111-1217-0151.

RESULTS

A total of 93 patients were included in the study, with an average age of 63 years and a predominance of females (68.8%; 64). Atrial fibrillation was the predominant indication for oral anticoagulation (92.5%; 86). The average number of medications used was 7.0. The average number of medications used in hospital 1 was 6.22 and in hospital 2 it was 6.1. The information collected is organized in Table 1, presenting the variables collected in the AC of hospitals 1 and 2.

Patients from both ACs, on hospitals 1 and 2, presented prescriptions with high MRCI. As for hospital CA 2, the majority of patients living in the capital have a therapeutic target of 2.0 to 3.0 and are polypharmacy (use 5 to 9 medications), as evidenced by Table 1 (65.4%; 72)).

Patients living in the metropolitan region had a higher percentage of adequate anticoagulation quality (TTR>60%), while patients living in Belo Horizonte had, for the most part, low TTR values, suggesting inadequate anticoagulation.

The calculation of the Odds Ratio (OR), P Value (P) and Confidence Interval (CI) for the Low, Moderate and High complexities presented in Table 1 were respectively: OR = 0.3525, P = 0.0350, CI = 0.1337 to 0.9292; OR = 0.5641, P = 0.0521, CI = 0.3165 to 1.0053; OR = 2.5821, P = 0.0011, CI = 1.4631 to 4.5568. Therefore, being from Hospital 1 is a protective factor, and the hospital is expected to be a reference for Chagas cardiomyopathy and for serious heart patients, for example, who have undergone heart surgery, unlike Hospital 2, which
basically cares for patients who have had a stroke or with some other vascular context.

### Table 1 - Variables collected in the AC of hospital 1 and hospital 2, Belo Horizonte, Minas Gerais, 2018-2019.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute frequency (n=93)</td>
<td>Absolute frequency (n=110)</td>
</tr>
<tr>
<td>Complexity of pharmacotherapy</td>
<td>Low (&lt; 9)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Moderate (≥ 9 and ≤ 16.5)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>High (&gt; 16.5)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Relative frequency (%)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>29</td>
</tr>
<tr>
<td>Therapeutic target</td>
<td>2 to 3</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>2.5 to 3.5</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Municipalit of residence</td>
<td>Belo horizonte</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Interior of Minas Gerais</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Metropolitan region</td>
<td>28</td>
</tr>
</tbody>
</table>

**DISCUSSION**

There was a predominance of females in the AC of hospital 1 (68.8%; 64), which is not in agreement with the literature, since atrial fibrillation is more common in men\(^5\). On the other hand, in the AC of hospital 2, the number of patients of both sexes was equal (50%), with an average age of 64 years for women and 67 for men.

The high rates of TTR from the metropolitan region when compared to residents of the capital may be related to the fact that the majority of the population is referred to urban centers, overloading access to health services, despite the idea of better infrastructure in these locations.

The high MRCI found for both AC patients from hospital 1 and 2 suggests that the identification of sociocultural specificities can help in the implementation of strategies that contribute to better quality of anticoagulation given the numerous factors that can interfere with the effectiveness and safety of warfarin. Among them, tools aimed at expanding the knowledge of anticoagulated patients about treatment, capable of minimizing the occurrence of thromboembolic events\(^6\).

The predominance of polypharmacy patients in the study is associated with greater complexity of pharmacotherapy, that is, different dosage regimens and pharmaceutical forms, characteristics found in the MRCI. Similar results were observed when translating the tool into Portuguese and Spanish\(^4,7\).

Polypharmacy is a growing condition in clinical practice, especially in the elderly\(^8\), since drug associations are recommended by guide-
lines for the management of several chronic diseases. However, it is necessary to ensure an optimized prescription based on the best available scientific evidence in order to minimize damage, increase longevity and improve quality of life.

In the context of anticoagulation with warfarin, polypharmacy must be evaluated with caution due to interactions with other medications and drug-food interactions, which may reduce or enhance the effects of the anticoagulant. Furthermore, factors such as adherence, high complexity of home pharmacotherapy, complex warfarin dosage regimen and access difficulties can interfere with INR values and, consequently, the quality of anticoagulation.

In order to minimize iatrogenic events, studies show that conventional care is less effective in controlling the occurrence of thromboembolic events and bleeding episodes when compared to follow-ups carried out in clinics specialized in anticoagulation control, such as those carried out in this study.

When analyzing the complexity of pharmacotherapy, it was found that the greater the number of medications in use, the greater the complexity of pharmacotherapy, corroborating a greater possibility of non-adherence due to the amount of information to be assimilated and memorized. Patients using 1 to 4 medications had, for the most part, a low complexity (88.9%; 16), while those using 5 to 9 medications had moderate complexities (71.4%; 35), and high (81.4%; 35). Those who use 10 medications or more have high pharmacotherapeutic complexity (18.6%; 8). The complexity of pharmacotherapy considers factors such as dosage, pharmaceutical form and the relationship between dose, food and administration actions. This concept is supported by another study that evaluated groups with high and low TTR, in which the majority of patients in both groups use between 5 and 9 medications. Therefore, the complexity of pharmacotherapy may not be directly related only to the number of medications prescribed, but rather to health literacy, low level of education, advanced age and multiple comorbidities, skills necessary for a correct understanding and adherence to pharmacotherapy.

When considering therapeutic targets for INR, a predominance of patients with target INR values of 2.0 - 3.0 was observed in all groups (high and low TTR and in the three pharmacotherapy complexity scores), therapeutic range recommended by international guidelines for patients with deep vein thrombosis (DVT), AF alone or associated with rheumatic valve disease or with biological prosthesis to minimize the risk of hemorrhage without increasing thrombotic risks. For patients with mechanical heart valve prostheses, INR values between 2.5 - 3.5 are targeted, a small minority of this study (7.3%; 8).

In contrast, in hospital 1, a percentage of patients with inadequate TTR had high MRCI. Therefore, special attention is recommended from health professionals in relation to this issue to adapt pharmacotherapy in order to promote adherence, in addition to investing in educational interventions that promote patient empowerment and the prevention of adverse events. These actions must include accessible vocabulary, legible writing and the use of drawings, colors or symbols to promote the control of pharmacotherapeutic parameters necessary for the individual’s health condition.

As observed, elderly people with polypharmacy had greater pharmacotherapeutic complexity. Polypharmacy favors drug interactions and can influence the patient’s TTR, in addition to increasing the risk of adverse effects.

It is noteworthy that the MRCI does not take into account individual characteristics such as age, sex, literacy level or comorbidities, making it advisable to carry out additional analyzes. Furthermore, this tool was developed without a score limit and cut-off number for classification, making it difficult to interpret the MRCI and its application in the clinical context.
The limitations of this study include the use of prescriptions delivered only by participants to score the MRCI, the lack of statistical data analysis and the lack of analysis of the therapeutic class of medications in use, preventing broader comparisons.

CONCLUSION

Through the study, it was noted that a large portion of patients had a high score on the Medication Regimen Complexity Index (MRCI), making it necessary to adopt educational measures and interventions according to the level of health literacy to facilitate understanding of the use of warfarin, in order to favor adherence to pharmacotherapy and avoid iatrogenic.

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