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Article

Use of a mobile application for the control of anticoagulation with warfarin: a cluster randomized controlled clinical trial – Ijui/RS/Brazil

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To evaluate the effectiveness of an anticoagulation protocol adapted in a mobile application (appG) for patients using warfarin. This was a cluster randomized controlled clinical trial carried out in basic health centers of Ijui, RS, Brazil, between April and October 2017. The appG was installed on the cell phones of all physicians belonging to the intervention group. Primary outcomes were bleeding and thrombosis, and secondary outcomes were changes in the dose of warfarin, use of new drugs, drug interactions, search for health services, and remaining on the target international normalized ratio. Thirty-three patients belonging to 11 basic health centers were included in this study. From these, 15 patients were in the intervention group which used the appG, and 18 were in the control group. After 6 months, patients in the appG group had fewer bleeding events (7% versus 50%, p-value=0.028) and a lower weekly dose of warfarin (29.3 ± 9.7 mg versus 41.7 ± 12.5 mg, p-value=0.030) when compared to the control group. The anticoagulation protocol adapted in a mobile app reduced bleeding in patients using warfarin.

Keywords: Mobile applications. Clinical trial. Warfarin. Outpatient monitoring.

INTRODUCTION

Among oral anticoagulants, warfarin is the most widely used drug in clinical practice (Serrano *et al*., 2013). Its therapeutic response varies, so laboratory monitoring is necessary at regular intervals to modify the dose if necessary, specially due to warfarin is widely used however major drawback is narrowly therapeutic index; under and over-dosing lead to complications and high healthcare costs (Ansell *et al*., 2008), and is associated with drug-drug interaction and drug and food's interaction (Colet, Amador, Heineck, 2018a). Such control seeks to ensure effectiveness and safety by preventing thromboembolic or bleeding events(Serrano *et al*., 2013), whose annual bleeding rates in warfarin users range from 15 to 25% (Patel *et al*., 2011; Granger *et al.,* 2011; Giugliano *et al.,* 2013).

The implementation of clinical protocols are among strategies to minimize warfarin-related adverse events special in cities where there is no other services to control oral anticoagulation, as it is shown in this research (Colet, Amador, Heineck, 2018b). These protocols have been used in several institutions with the aim of standardizing and guiding health professionals regarding the correct use of coumarins (Castro, Heineck, 2012). However, complex protocols requiring manual calculations for adjustments are difficult to adapt or follow. In addition, the use of support health technologies facilitates the decision-making process and improves the management of chronic diseases (Burke *et al*., 2015). Some international medical guidelines have applications for dose calculation and guidelines regarding the use of anticoagulants, however, all of them are in the English language and have algorithms validated with populations that often do not reflect the reality in Brazil (Raghu *et al*., 2015;

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Zhao, Kansal, 2009; Stephan *et al*., 2017). Additionally, no validated Portuguese-language application (appG) has been found in the literature to assist in the decision-making process regarding the dosage of warfarin, specifically in primary health care.

Considering the above, the objective of this study was to evaluate the efficacy of a warfarin protocol, adapted for a mobile appG, in patients using warfarin. It is believed that the mobile appG can provide more safety in the use of warfarin in primary health care.

MATERIAL AND METHODS

Study design

This was a two-arm, randomized, and controlled clinical trial by cluster carried out in basic health centers (BHCs). Physicians working in 11 BHCs belonging to the Municipal Health Department of Ijuí, Rio Grande do Sul, Brazil were eligible for this study, no sample calculation was performed since all the patients that fit the inclusion criteria were invited to participate in the study.This research was conducted from April to October 2017. The researchers generated a random sequence of numbers using Excel® in order to allocate the BHCs. Five BHCs were selected for the control group (CG) and 6 BHCs for the intervention group using the mobile health app (appG). In this study, the patients who used warfarin, the doctors who worked in the BHCs, and the researchers who followed-up with the patients were blinded.

Participants

First, all BHCs in Ijuí were identified. Then (i) the appG was installed for physicians of the BHCs where the intervention was selected to take place, and (ii) the patients who attended these BHCs and made long use of warfarin were identified through medical records.

BHCs were included in this study if they were located in the city of Ijuí. Of these BHCs, all patients with long use of warfarin were selected for home follow-up. BHCs that did not deliver warfarin in the six months prior to the start of this study, or patients who refused to participate in the study were excluded. The medical indication of use for more than six months was considered chronic, without limiting the maximum time of use.

Interventions

A mobile health appG, which was developed for the control of oral anticoagulation, was installed on the private cell phone of all physicians working in the BHCs which were randomly allocated for the appG. The installation of the appG was performed by the researcher on the day scheduled with each physician. This researcher also trained the physicians how to use the appG for patients who use the anticoagulant and were treated at the BHCs. The CG consisted in maintaining the anticoagulant prescription in the routine manner of the BHCs.

The mobile health appG was developed by the Institute of Cardiology of Porto Alegre. The adapted version, used in this study, included the anticoagulant dose calculator which was developed based on an anticoagulation protocol used at the *Hospital de Clínicas de Porto Alegre* (Hospital of Clinics of Porto Alegre, 2012).

The appG version used in this study consisted of a single screen in which the target international normalized ratio (INR) and the dose of the pill used were selected. Then the total weekly dose of the drug and the current INR were entered for each patient. It should be noted that the appG considers the clinical situation for which the drug is being used: (1) target INR between 2.0 and 3.0; and (2) target INR between 2.5 and 3.5. Versions have been developed for iOS and Android operating systems.

On the first visit, patients from both the appG and the CG clusters who use an anticoagulant were submitted to a clinical evaluation. During the six-month period (April to October 2017), these patients were monitored monthly through follow-ups in their homes to evaluate adverse events, therapeutic control, use of new drugs, and any search for health services. The appG was installed by the researcher on the cell phones of all participating physicians. The patients' evaluations were carried out monthly by researchers who have previously received training in order to standarize procedures.

Outcomes

The primary outcome variables were bleeding and thrombosis, which were identified in the patients' reports during the monthly home follow-up and confirmed by checking the medical records at the BHCs. Bleeding was not classified regarding severity, and only its occurrence was monitored. Thrombosis was defined as the presence of central or systemic embolism as well as the diagnosis of deep vein thrombosis. Secondary outcomes included the need for changes in the dose of warfarin, use of new drugs, drug interactions, search for health services, and remaining on the target INR. The search for health service was evaluated because its increased search may be associated with adverse events

The INR data collected during follow-up were used to calculate the time in therapeutic range (TTR), according to the validated and adapted method, considering adequate values from 2.5 to 3.5 (Schimidt, Spechman, Ansell, 2003). Lower values were defined as subtherapeutic and higher values as supratherapeutic. TTR was the variable defined for therapeutic control analysis.

Sample size

No calculation of the sample size was performed since all patients with long use of warfarin in the public health system of the city of Ijuí, RS were included in the study.

Sequence generation

The random allocation sequence was created using computer generated numbers in Excel®. Randomization by block was performed, where the BHCSs included were considered the blocks.

Implementation

The researchers carried out the generation of the random allocation sequence, the enrollments of participants, and the assignment of their interventions.

Blinding

In this study, the patients who used warfarin, the doctors who worked in the BHCs, and the researchers who followed-up the patients were blinded.

In the intervention group, the definition of warfarin doses by physicians was performed using the appG. In the control group, the usual prescription method was maintained.

Statistical analysis

For data analysis, descriptive statistics measures were used, such as mean ± standard deviation (SD) for quantitative variables, and absolute and relative frequency for qualitative variables. The normality of the data was tested using the Kolmogorov-Smirnov test. The qualitative variables (gender, level of education, reason for warfarin use, symptoms, bleeding, and thrombosis) were analyzed using the Pearson's chi-square test, as appropriate. The quantitative variables (age, body mass index, duration of use, dose, number of medications, number of interactions, and TTR) were analyzed using the Student's t-test for independent samples. For all tests, a 5% level of significance was considered. The software used for data analysis was the Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The study was approved by the Research Ethics Committee of the Regional University of Northwestern Rio Grande do Sul, under the document number 850.054/2016 (CAAE 61718916.8.0000.5350). The study was registered in the Brazilian Clinical Trials Registry (ensaiosclinicos.gov.br) under the number RBR-5NCT6D.

RESULTS

A total of 11 BHCs were included in this study, which consisted of 33 patients who participated and were followed-up, and 15 patients who were excluded, as shown in Figure 1. The mean age of the studied patients

was 65.0 ± 11.2 years. There was a predominance of women (54.5%). The main self-reported reason for the prescription of oral anticoagulants was the presence of metallic heart valve prosthesis (51.5%). The mean weekly dose of warfarin in the studied population was 34.5 ± 12.1 mg. Approximately 50.0% of the patients reported some type of bleeding in the month prior to the beginning of this data collection.

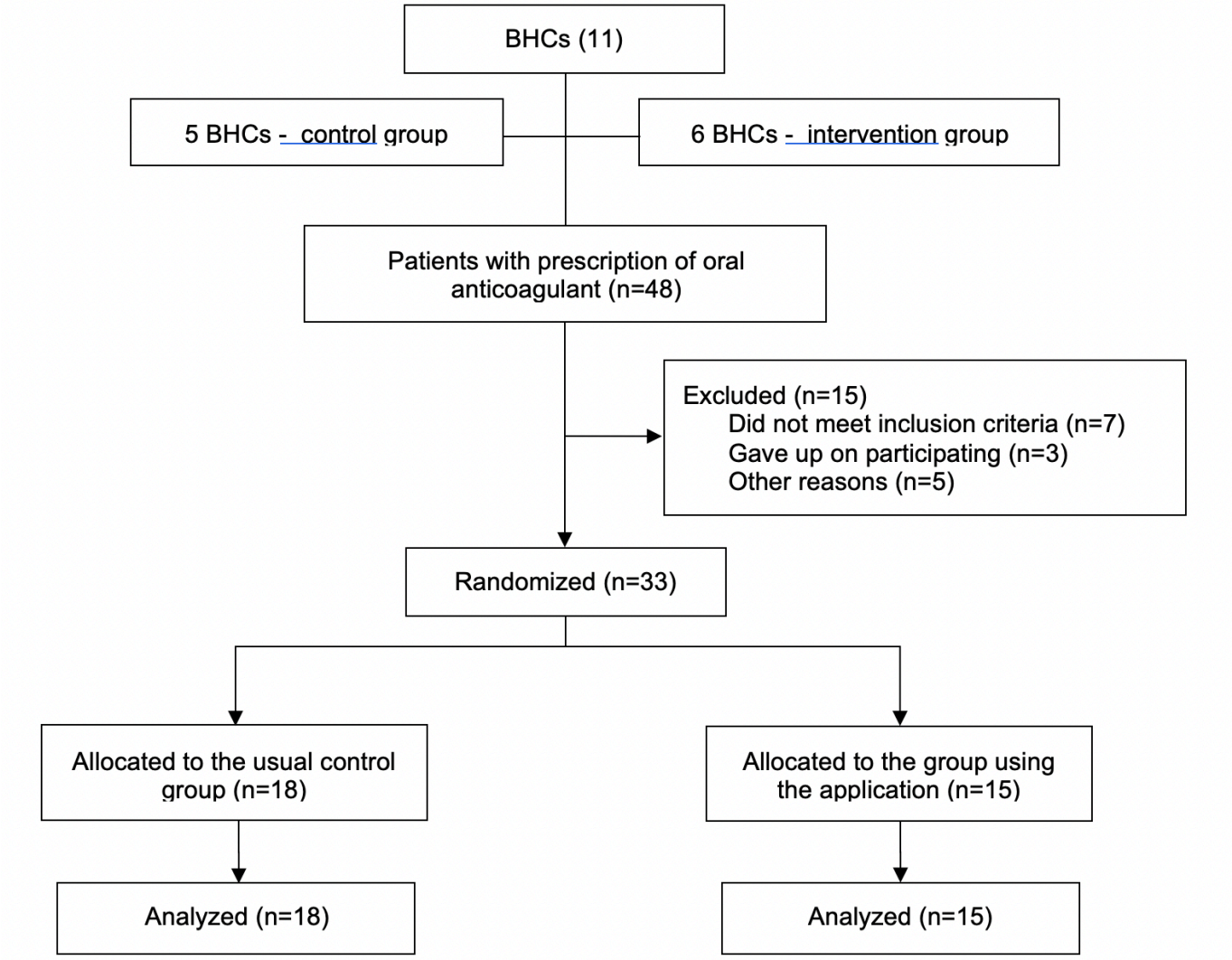

FIGURE 1 - Recruitment and randomization of basic health centers (BHCs) and patients allocated to each study group.

The baseline clinical characteristics and variables related to the use of warfarin are presented in Table I.

TABLE I - Baseline clinical characteristics and variables related to the use of warfarin

	CG n = 18	**appG n = 15**
Males, n (%)	8 (44.4%)	7 (46.7%)
Age, years (SD)	65.0 (± 12.9)	65.7 (± 10.2)
BMI, kg/m^2 (SD)	27.0 (± 4.5)	25.9 (± 8.2)
Level of education, n (%)		
Elementary - incomplete	11 (61.1)	10 (66.7)
Elementary - complete	3 (16.7)	2 (13.3)
High school - complete	2 (11.1)	3 (20.0)
Higher education	2 (11.1)	0 (0.0)
Duration of warfarin use, years (SD)	9.0 (± 4.2)	9.0 (± 4.3)
Reason for using warfarin, n (%)		
Valve/pacemaker	8 (44.4)	9 (60.0)
Prevention and treatment of thrombosis	7 (38.9)	2 (13.3)
Stroke	0 (0.0)	3 (20.0)
Arrhythmia	3 (16.7)	1 (6.7)
Total weekly dose of warfarin, mg (SD)	36.6 (± 16.6)	31.9 (± 10.6)
Symptoms, n (%)		
Pain	6 (33.3)	5 (33.3)
Tiredness	11 (61.1)	7 (46.7)
Edema	1 (5.5)	5 (33.3)
Palpitations	3 (16.7)	4 (26.7)
Cough	1 (5.5)	0 (0.0)
Report of bleeding, n (%)	**9 (50.0)**	**7 (46.7)**

CG - control group; appG - mobile health application group; BMI - body mass index

The prevention of adverse events was superior when using the mobile health appG compared to the control group. The incidence of bleeding was 50.0% in the CG, and 6.7% in the appG (p-value=0.028). There were no thrombotic events in any of the studied patients (Table II).

TABLE II - Primary and secondary outcomes in the control group and in the mobile health application group

	CG n = 18	appG n = 15	p-value
Primary outcome			
Bleeding, n (%)	9 (50.0)	1 (6.7)	0.028
Thrombosis, n (%)	0 (0.0)	0 (0.0)	-
Secondary outcomes			
Change in warfarin dose, n (%)	5 (27.8)	7 (46.7)	0.271
Use of new drugs, n (%)	5 (27.8)	8 (53.3)	0.692
Number of drugs, (SD)	5.1 (± 1.6)	6.5 (± 2.6)	0.048
Drug interactions, (SD)	1.8 (± 0.8)	2.1 (± 1.5)	0.536
Total weekly dose of warfarin, mg (SD)	41.7 (± 12.5)	29.3 (± 9.7)	0.030
TTR ‡, % (SD)	62.5 (± 36.5)	68.9 (± 39.4)	0.513

CG - control group; appG - mobile health application group; TTR ‡ - time in therapeutic range; Fisher's exact test and Student's t test for independent samples, as appropriate.

The therapeutic control of the INR levels, expressed in TTR, was not significantly different between the groups. Although not significantly different, a greater number of changes in warfarin dosage was observed in the appG, resulting in a significantly lower total weekly dose of the drug when compared to the CG (p-value=0.030), at the end of the follow-up. There was a greater use of other drugs associated with warfarin in the appG, when compared to the CG (p-value=0.048) (Table II).

DISCUSSION

The use of a mobile app by physicians improved the control of the oral anticoagulant because it significantly reduced the incidence of bleeding and the total weekly dose of warfarin in patients taking warfarin in primary health care, but did not interfere with the TTR.

A possible explanation for not observing a difference in INR control rate during the follow-up can be attributed to the sample size and the duration of follow-up, as well as other bleeding related variables that were not evaluated in this study, like age, and other clinical factors.

The bleeding rate in appG was lower than shown in international studies which demonstrated annual bleeding rates of 15 to 26% among warfarin users (Granger *et al.,* 2011; Giugliano *et al.,* 2013). In a Brazilian study, carried out in an anticogulation outpatient clinic in Porto Alegre, RS, the annual bleeding rate among those using warfarin was 18.8% (Leiria *et al.,* 2010). On the other hand, the bleeding incidence in the control group was higher than those found in the previously mentioned studies (Giugliano *et al.,* 2013, Leiria *et al.,* 2010, Castro, Heineck, 2012) which demonstrates the positive impact of the use of the mobile health appG on the control of oral anticoagulation in warfarin patients in primary health care. The control of bleeding in patients using anticoagulants is necessary since such an outcome is related to weaker adherence to treatment, higher rates of avoidable hospitalizations and mortality, and consequently, higher costs involved with the treatment (Platt *et al*, 2010).

The risk of bleeding is directly related to the intensity of the anticoagulation, as assessed by the high INR values (Inoue *et al.,* 2018). In our study, although a reduction in the bleeding rate was seen in the appG, no significantly

difference was observed in the INR values between the groups. This may be related to the sample size and follow-up period. Furthermore, INR and bleeding data were not always collected on the same date. This was because INR was not always calculated at the time of bleeding, or when it was, the patient did not keep a copy of the exam results. These facts may have caused the differences between the results found. Even with such limitations, the INR data in the appG were similar to those found in previous studies from an anticoagulation clinic (Agnelo, Alexandra, Matias, 2014) as well as a meta-analysis with patients followed-up in basic health care in European countries, which demonstrated a therapeutic INR in 57% of time (Van Walraven *et al.,* 2006).

The bleeding rate, as well as other outcomes in warfarin patients, depends on factors other than the INR control, such as: use of associated drugs, dietary interactions, and individual characteristics of the patients (Tadros, Shakib, 2010). In our study, such variables were not analyzed as potential factors of the outcome, and may justify the data found.

There was a difference between CG and sG in the total weekly dose of warfarin in patients taking this drug in primary health care, with higher dose in CG group. Studies have shown that the mean warfarin dose is 31.1 to 34.5 mg/week, with a variability of 7.5 to 105 mg/week (Pelegrino *et al*., 2010). It should be noted that smaller weekly doses do not indicate better therapeutic safety or efficacy, since the weekly dose is influenced by clinical factors (age, race, body weight, sex, concomitant use of medications, comorbidities, diet, nutritional status) (Serrano *et al*., 2013, Colet, Amador, Heineck, 2018) and genetic factors (Furie, 2013). The presence of genetic polymorphisms, especially the CYP2C9 and VKORC1 genotypes, causes a reduction of the metabolism or an increase of warfarin sensitivity, making these patients require lower doses of the drug (Suarez-Kurtz, Botton, 2015).

The results showed that the use of a mobile app by physicians significantly reduced the rate of bleeding. Although warfarin is effective in reducing thromboembolic events, it requires periodic monitoring because it causes a risk of bleeding. This fact has an influence on why many patients do not receive a warfarin prescription, even when they need it. Studies demonstrated a lower rate of indication for anticoagulants in different populations with a risk of thromboembolic events due to the difficulty of controlling adverse events.[22-23] Therefore, the use of the mobile appG may be an affordable technological option for proper control.

Only 50% of patients who could benefit from the use of warfarin actually had their were compliant (Go *et al*., 1999). Additionally, approximately a third of patients with atrial fibrillation and indication for an anticoagulant either did not initiate or abandoned the treatment early due to high risk (Bartholomay *et al*., 2014). Hence, the use of an appG as a support tool for the prescription of warfarin in basic health care can minimize cases of under-prescription of this drug and increase the prescriber's safety and the patient's adherence to the treatment.

The implementation of specialized services for anticoagulation improves patient's adherence and knowledge about the drug effects. Consequently, it allows longer time within the therapeutic range resulting in greater safety and efficacy, as well as less of a need to seek secondary or tertiary treatments (Mansur *et al*., 2012). Our study aimed to demonstrate that an oral anticoagulation protocol adapted in an appG can be an alternative in the primary health care to reduce the occurrence of hemorrhagic events in Brazilian municipalities that do not have anticoagulation clinics.

The use of an appG, which is often used in European countries, may be an important tool to initiate a new type of follow-up in Brazil. It consists of patients being responsible for the control and monitoring of their anticoagulation (Jenner *et al*., 2015). There are meta-analyses demonstrating a significantly reduction in thromboembolic events (Henegahn, Ward, Perera, 2012, Christensen *et al.,* 2017), and in mortality (Christensen *et al*., 2017) associated with self-control.

Some limitations of this study are: great variability in the time of warfarin use among participants, it can not be controlled if physicians always accepted the dose adjustment proposed by the application, bleeding was not categorized by severity and INR was not always performed in the date of bleeding.

CONCLUSION

The adapted anticoagulation protocol in a mobile appG reduced bleeding in patients using warfarin in primary health care. The use of this tool seems to have provided greater safety to patients, so that any necessary changes in the dosage could be performed. It is fundamental to seek the development of tools to ensure greater effectiveness and safety for warfarin users and professionals responsible for its prescription, and the mobile appG is shown to be a viable tool.

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