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Pharmacotherapeutic follow-up of patients on warfarin in primary care: randomized clinical trial

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Summary

Aim: To evaluate the impact of pharmacotherapeutic follow-up on bleeding, time in therapeutic range (TTR), thrombotic events, general adverse events, hospitalizations, drug interactions and average number of medications used in patients taking warfarin in the Brazilian public healthcare system. **Methods:** A randomized clinical trial was conducted with individuals divided into two groups (intervention group [pharmacotherapeutic follow-up] and control group) who received at-home visits over an eight-month period. **Results:** 38 individuals (21 in the intervention group and 17 in the control group) concluded the study. Fewer number of cases of bleeding was found in the group that received pharmacotherapeutic follow-up, but no significant association was found between these variables. No significant association was found between pharmacotherapeutic follow-up and TTR. The intervention group had a greater frequency in the therapeutic range for capillary INR but not for laboratory INR. Reductions were found in the intervention group with regards to general adverse events, the use of medications and drug interactions, whereas no reduction was found in hospitalizations. **Conclusions:** Based on the findings of the present study, pharmacotherapeutic follow-up did not exert an influence on bleeding or

TTR. However, reductions were found in adverse events and drug interactions, which can contribute to the rational use of medicines and could result in lower care costs for patients requiring blood thinners.

Keywords: Warfarin, pharmaceutical care, primary health care.

Resumo

Acompanhamento farmacoterapêutico de pacientes em uso de varfarina na atenção primária: ensaio clínico randomizado

Objetivo: Avaliar o impacto do acompanhamento farmacoterapêutico sobre sangramento, tempo de intervalo terapêutico (TTR), eventos trombóticos, eventos adversos gerais, internações, interações medicamentosas e número médio de medicamentos utilizados em pacientes em uso de varfarina no sistema público de saúde brasileiro. **Métodos:** Foi realizado um ensaio clínico randomizado com indivíduos divididos em dois grupos (grupo intervenção [acompanhamento farmacoterapêutico] e grupo controle) que receberam visitas domiciliares durante um período de oito meses. **Resultados:** Trinta e oito indivíduos (21 no grupo intervenção e 17 no grupo controle) concluíram o estudo. Um menor número de casos de sangramento foi encontrado no grupo que recebeu acompanhamento farmacoterapêutico, mas não foi encontrada associação significativa entre essas variáveis. Não foi encontrada associação significativa entre seguimento farmacoterapêutico e TTR. O grupo intervenção apresentou maior frequência na faixa terapêutica para INR capilar, mas não para INR laboratorial. Foram encontradas reduções no grupo intervenção em relação aos eventos adversos gerais, uso de medicamentos e interações medicamentosas, enquanto não houve redução nas internações. **Conclusões**: Com base nos achados do presente estudo, o acompanhamento farmacoterapêutico não exerceu influência sobre sangramento ou TTR. No entanto, foram encontradas reduções nos eventos adversos e interações medicamentosas, o que pode contribuir para o uso racional de medicamentos e pode resultar em menores custos assistenciais para pacientes que necessitam de anticoagulantes.

Palavras-chaves: Varfarina, atenção farmacêutica, atenção primária à saúde.

Resumen

Seguimiento farmacoterapéutico de pacientes en tratamiento con warfarina en atención primaria: ensayo clínico aleatorizado

Objetivo: Evaluar el impacto de la monitorización farmacoterapéutica sobre el sangrado, el tiempo de intervalo terapéutico (TTR), los eventos trombóticos, los eventos adversos generales, las hospitalizaciones, las interacciones medicamentosas y el número medio de medicamentos utilizados en pacientes que utilizan warfarina en el sistema de salud pública brasileño**. Métodos:** Se realizó un ensayo clínico aleatorizado con sujetos divididos en dos grupos (grupo de intervención [seguimiento farmacoterapéutico] y grupo control) que recibieron visitas domiciliarias durante un período de ocho meses. **Resultados:** Treinta y ocho sujetos (21 en el grupo de intervención y 17 en el grupo de control) completaron el estudio. Se encontró un menor número de casos de sangrado en el grupo que recibió seguimiento farmacoterapéutico, pero no se encontró asociación significativa entre estas variables. No se encontró asociación significativa entre seguimiento farmacoterapéutico y TTR. El grupo de intervención tuvo mayor frecuencia en rango terapéutico para INR capilar, pero no para INR de laboratorio. Se encontraron reducciones en el grupo de intervención con respecto a los eventos adversos generales, el uso de medicamentos y las interacciones medicamentosas, mientras que no hubo reducción en las hospitalizaciones. **Conclusiones:** Con base en los hallazgos del presente estudio, el seguimiento farmacoterapéutico no influyó en el sangrado ni en la RTT. Sin embargo, se encontraron reducciones en los eventos adversos y las interacciones medicamentosas, lo que puede contribuir al uso racional de los medicamentos y puede resultar en menores costos de atención para los pacientes que requieren anticoagulantes.

Palabras clave: Warfarina, atención farmacéutica, atención primaria de salud.

Introduction

Warfarin is the most widely prescribed oral anticoagulant in primary care due to its proven effectiveness and low cost. However, it is a potentially hazardous drug due to the narrow therapeutic window and variable response [1], which can lead to adverse reactions and preventable hospital admissions [2, 3].

A single-center cohort study involving patients on warfarin found a higher incidence of bleeding compared to other studies, which was associated with exposure to warfa-

rin-related drug interactions [4] demonstrating the need for interventions to minimize such adverse events and the promotion of the safer use of this anticoagulant.

Follow-up through pharmaceutic care could improve the quality of treatment with warfarin [5, 6] and could be an effective strategy for preventing, identifying and solving problems related to pharmacotherapeutic treatment [7]. Studies conducted in other countries have demonstrated the benefits of the engagement of the pharmacist in oral anticoagulation with warfarin [8, 9]. In Brazil, few studies have addressed the follow-up of patients on blood thinners [10], especially studies on at-home pharmacotherapeutic follow-up.

The aim of the present study was to evaluate the impact of pharmacotherapeutic follow-up on bleeding, time in the therapeutic range, thrombotic events, general adverse events, hospitalizations, drug interactions and average number of medications used in patients taking warfarin in the Brazilian public healthcare system.

Material And Methods

Study design

A randomized, parallel, controlled, clinical trial was conducted comparing the results of pharmacotherapeutic follow-up in patients on warfarin in the public healthcare system to a control group without pharmacotherapeutic follow-up. The flowchart of the randomization procedure in accordance with the *Consolidated Standards of Reporting Trials* (CONSORT) is shown in Figure 1.

This investigation is linked to a study by the *Universidade Regional do Noroeste do Estado do Rio Grande do Sul* entitled "Evaluation of the effectiveness of a protocol for patients on anticoagulants in the public healthcare system of the municipality of Ijuí/RS" (approved through process number: 1.850.054/2016 and PPSUS/FAPERGS 002/2017). Data were collected through monthly visits over an eight-month period between September 2018 and April 2019.

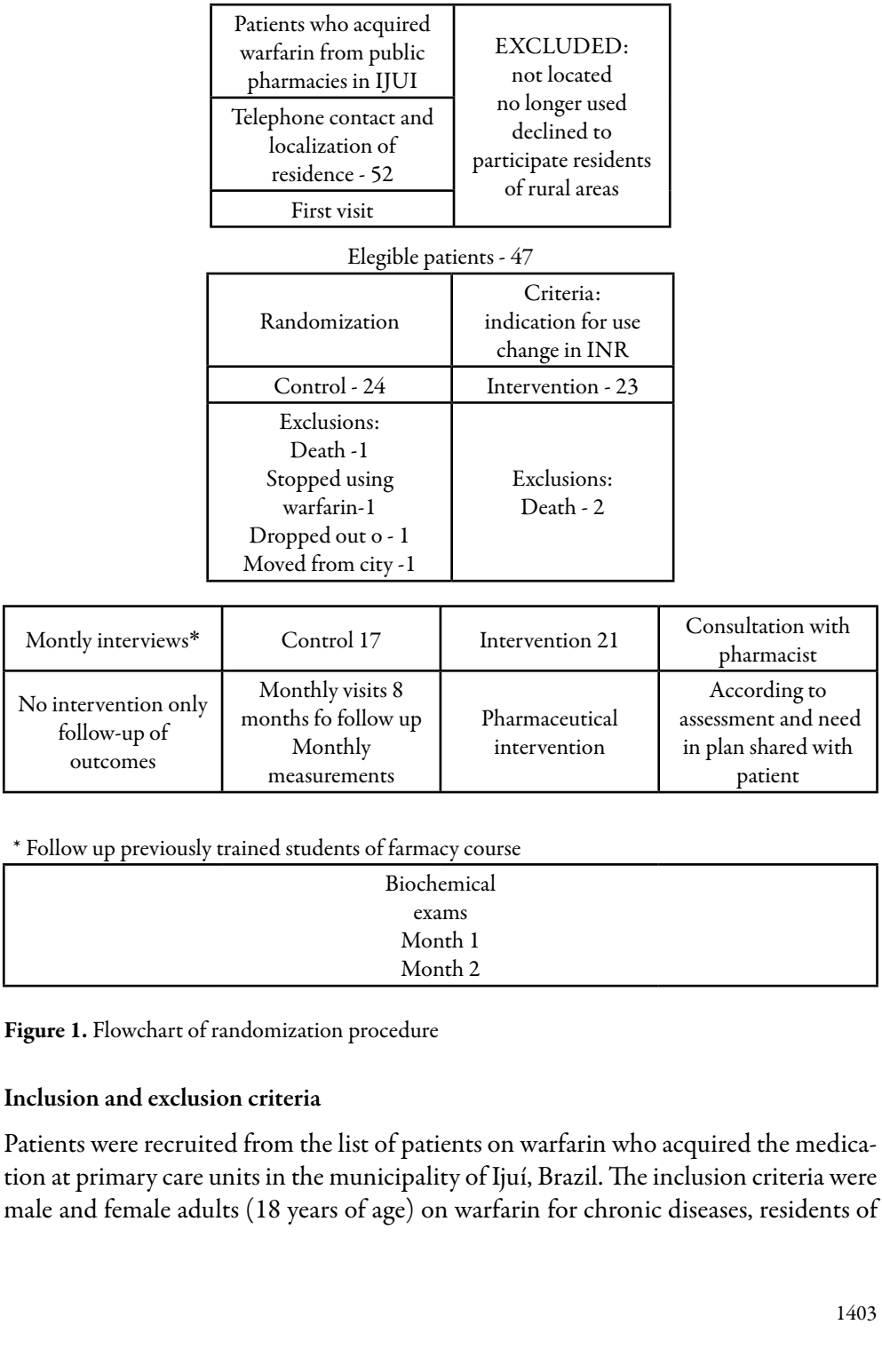

Figure 1. Flowchart of randomization procedure

Inclusion and exclusion criteria

Patients were recruited from the list of patients on warfarin who acquired the medication at primary care units in the municipality of Ijuí, Brazil. The inclusion criteria were male and female adults (18 years of age) on warfarin for chronic diseases, residents of

urban areas, having been seen at a primary care unit in the municipality and having received at least seven follow-up visits during the study.

Sample size and randomization

Fifty-two patients were identified, 47 of whom were eligible for the study and randomized to a control group (n=24) and intervention group (n=23). The randomization of the patients was performed using Microsoft Excel Software 2016. To minimize bias, the groups were stratified according to the indication for the use of warfarin and alterations in the INR. These data were obtained during the initial interview. The allocation sequence was generated by the researchers, as blinding was not performed. Both groups underwent an initial and final evaluation using the same protocol. The procedures for the control and intervention groups are described below.

Control group (CG): monthly at-home visits by previously trained researchers with no pharmaceutical intervention.

Intervention group (IG): pharmaceutical intervention by a previously trained researcher during monthly at-home visits. After the initial evaluation, a care plan was designed with the participation of the patient and pharmaceutical interventions were performed in accordance with the needs of each patient. The care plan was designed following the recommendations of the *Health Ministry for Pharmaceutical Care in Primary Health Care* [11]. An agreement was forged with the patient on the actions to be performed and the definition of the therapeutic goals.

Data collection

At the participants' homes, the researchers administered questionnaires for the collection of data. Questionnaire 1 addressed socioeconomic aspects, pharmacotherapy and comorbidities. Questionnaire 2 was used for monthly follow-up. The data were used to characterize the population of warfarin users based on sociodemographic and pharmacotherapeutic data, perform follow-up and guide counseling.

Measures

a. *INR – laboratory:* determined by an outsourced laboratory with at-home collections from the participants in September 2018 and April 2019. Patients with INR results within the reference values according to the reason for warfarin use were considered to be within the adequate therapeutic range [12].

b. *INR – capillary:* determined using the Roche® Coagucheck device during visits in October, December and February.

c. *Bleeding, thrombosis, hospitalizations:* The incidence of these events was verified through a direct question posed to the participant during each visit (self-report). All hospitalizations were considered and not only those related to warfarin use.

d. *Time in therapeutic range (TTR)*: calculated considering laboratory and capillary INRs. The calculation for each period was performed by the difference between two consecutive INR values and the target range [13].

e. *Adverse events:* Using a list of the most common symptoms that may be caused by medications in primary care [14] the following statement was made to the participants: "I am now going to read you a list of common problems and I would like you to tell if you are feeling or have felt any of them in the past month."

f. *Drug interactions:* Using the Drug Interactions tool from Micromedex® Solutions, warfarin-related interactions were identified and classified as 1) increased risk of bleeding and 2) increased risk of thrombosis.

Outcomes

The primary outcomes were the minimization of the incidence of bleeding and an increase in the TTR. The secondary outcomes were the minimization of thrombotic and other events and reductions in hospitalizations, drug interactions and the number of medications.

Statistical analysis

All analyses were conducted using the *Statistical Package for the Social Sciences* (SPSS Inc., Chicago, IL, USA), version 23.0. The normality of the data was tested using the Kolmogorov-Smirnov test. Continuous data were expressed as mean and standard deviation or median and interquartile range. Categorical data were expressed as absolute and relative frequency. Associations between two or more qualitative variables were investigated using either Pearson's chi-square test or Fisher's exact test. For quantitative variables, comparisons of means were performed using the Student's t-test for independent parametric variables and the Mann-Whitney and Kruskal-Wallis tests for independent nonparametric variables. The significance level was set at 5%.

Results And Discussion

Fifty-two individuals were identified, five of whom were excluded for not meeting the eligibility criteria and 47 were randomized to the different groups. Thirty-eight individuals (21 in the IC and 17 in the CG) concluded the study Table 1).

Among the patients who concluded the study, mean age was 67.42±13.74 years. The other characteristics of the sample are displayed in Table 1. The main reason for the use of warfarin was the prevention of thrombosis. Time on warfarin ranged from one to 20 years. The most frequent comorbidity was hypertension in both groups. The only significant difference between the two groups regarded obesity (p=0.010), which was more frequent in the IG (Table 1).

Table 1. Characterization of individuals in control and intervention (pharmacotherapeutic follow-up) groups on warfarin in public healthcare system. Ijuí, RS, Brazil, 2018

		Groups		
		Control n=17	**Intervention n=21**	**p**
		n (%)	n (%)	
Sex	Male	7 (41.2)	7 (33.3)	0.618&
	Female	10 (58.8)	14 (66.7)	
Marital status	Single	2 (11.8)	2 (9.5)	0.789#
	Married	7 (41.2)	12 (57.1)	
	Separated/divorced	4 (23.5)	3 (14.3)	
	Widowed	4 (23.5)	4 (19.0)	
Skin color	White	16 (94.1)	17 (89.5)	0.543#
	Brown	1 (5.9)	2 (10.5)	
Schooling	Illiterate	0 (0.0)	3 (14.3)	0.146#
	Incomplete/complete primary school	9 (56.2)	9 (42.9)	
	Incomplete/complete high school	6 (37.6)	3 (14.3)	
	Complete higher education	1 (6.2)	1 (4.8)	
Morbidity/ Risk factors	Diabetes mellitus	5 (29.4)	7 (33.3)	0.796
	Dyslipidemia	10 (58.8)	9 (42.9)	0.328
	Hypertension	16 (94.1)	20 (95.2)	0.701
	Coronary artery disease	12 (70.6)	18 (85.7)	0.230
	Chronic kidney failure	2 (11.8)	0 (0.0)	0.193
	Obesity	2 (11.8)	11 (52.4)	0.010*
	Vascular disease	7 (41.2)	4 (19.0)	0.128
	Sedentarism	1 (5.9)	2 (9.5)	0.581
	Smoking	10 (58.8)	11 (52.4)	0.691

Legend: # - Fisher's exact test; & - chi-square test; * $p < 0.05$.

Fewer cases of bleeding occurred in the IG but no significant association was found with pharmacotherapeutic follow-up (p=0.389). Throughout the entire eight-month study, eight patients in the CG (53.3%) and seven in the IG (46.7%) had at least one episode of bleeding.

Table 2 displays the data on the incidence of bleeding and thrombosis throughout the study. Patients in the IG with episodes of bleeding received the following interventions: sent to undergo laboratory INR exam, sent to physician at reference primary care unit, counseling on non-pharmacological measures, review of pharmacotherapy, and creation of medication posology calendar, pictorial labels/instructions and medication storage organizer to assist in administration of medications. Adjustment of the warfarin dose was suggested for six patients and the dose was altered in one patient after contact with the primary physician, corresponding to a 16.7% acceptance rate of this pharmaceutical intervention.

Table 2. Bleeding and thrombosis in control and intervention (pharmacotherapeutic follow-up) groups of patients on warfarin in public healthcare system. Ijuí, RS, Brazil, 2019

		Bleeding			**Thrombosis**		
		Yes	**No**	*P*	**Yes**	**No**	*p*
Month	R	n (%)	n (%)		n (%)	n (%)	
01	*Control*	5 (29.4)	12 (70.6)	0.052	1 (5.9)	16 (94.1)	0.459
	Intervention	1 (4.8)	20 (95.2)		0 (0.0)	20 (100)	
02	*Control*	3 (17.6)	14 (82.4)	0.420	2 (11.8)	15 (88.2)	0.204
	Intervention	2 (10.0)	18 (90.0)		0 (0.0)	20 (100)	
03	*Control*	2 (12.5)	14 (87.5)	0.333	0 (0.0)	17 (100)	-
	Intervention	5 (23.8)	16 (76.2)		0 (0.0)	21 (100)	
04	*Control*	2 (11.8)	15 (88.2)	0.604	0 (0.0)	17 (100)	0.299
	Intervention	3 (14.3)	18 (85.7)		2 (9.5)	19 (90.5)	
05	*Control*	1 (5.9)	16 (94.1)	0.387	1 (5.9)	16 (94.1)	0.701
	Intervention	3 (14.3)	18 (85.7)		1 (4.8)	20 (95.2)	
06	*Control*	2 (11.8)	15 (88.2)	0.419	0 (0.0)	17 (100)	-
	Intervention	1 (4.8)	20 (95.2)		0 (0.0)	21 (100)	
07	*Control*	4 (23.5)	13 (76.5)	0.112	3 (17.6)	14 (82.4)	0.081
	Intervention	1 (4.8)	20 (95.2)		0 (0.0)	21 (100)	
08	*Control*	1 (6.7)	14 (93.3)	0.627	0 (0.0)	15 (100)	0.364
	Intervention	1 (4.8)	20 (95.2)		0 (0.0)	21 (100)	

Note: Some patients in control group did not receive at-home visits in months 1, 2, 5 and 8; Fisher's exact test for all analyses; * $p < 0.05$.

TTR results ranged from 47.1 to 41.2% in the CG and 38.1 to 28.6% in the IG, but this difference did not achieve statistical significance (p=0.901). No significant differences between groups were found with regards to median TTR (p=0.271), bleeding (p=0.392) or thrombosis (p=0.409).

Table 3 displays the percentages of patients according to the therapeutic range of laboratory and capillary INR. Patients with laboratory INR below the target range predominated in both groups. Moreover, no statistically significant difference between groups was found regarding capillary INR, but a greater frequency of normal values was found in the three analyses conducted in the IG.

Table 3. Frequencies according to therapeutic range of INR[a] in control and intervention (pharmacotherapeutic follow-up) groups of patients on warfarin in public healthcare system. Ijuí, RS, Brazil, 2019

			INR[a]			
			L[b]	N[c]	H[d]	
	Month	**Groups**	**n (%)**	**n (%)**	**n (%)**	**p**
INR Laboratory 01	01	*Control*	10 (58.8)	7 (41.2)	0 (0.0)	0.154
		Intervention	11 (52.4)	6 (28.6)	4 (19.0)	
INR Laboratory 02	08	*Control*	9 (52.9)	8 (47.1)	0 (0.0)	0.601
		Intervention	12 (57.1)	8 (38.1)	1 (4.8)	
INR Coaguchek 01	01	*Control*	6 (37.5)	3 (18.8)	7 (43.8)	0.841
		Intervention	8 (40.0)	5 (25.0)	7 (35.0)	
INR Coaguchek 02	02	*Control*	4 (30.8)	4 (30.8)	5 (38.5)	0.755
		Intervention	6 (28.6)	9 (42.9)	6 (28.6)	
INR Coaguchek 03	04	*Control*	4 (28.6)	6 (42.9)	4 (28.6)	0.340
		Intervention	3 (15.8)	13 (68.4)	3 (15.8)	

Legend: a – INR = international normalized ratio; b – low; c – normal; d – high; * $p < 0.05$, Fisher's exact test for all analyses.

All adverse events investigated were significantly less frequent in the IG. The most frequent adverse event in the IG was headache, with 11 patients (52.4%) reporting this problem at the initial evaluation and three (30%) reporting at the end of the follow-up (p=0.02) (Table 4).

Table 4. Adverse events in control and intervention (pharmacotherapeutic follow-up) groups of patients on warfarin in public healthcare system at onset and end of study. Ijuí, RS, Brazil, 2019

	Initial			Final			
	CG	IG	p[a]	CG	IG	p[a]	p[b]
Adverse event	n (%)	n (%)		n (%)	n (%)		
Headache	3 (17.6)	11 (52.4)	0.027*	3 (30)	3 (30)	0.301	0.002*
Itching	3 (17.6)	4 (19.0)	0.912	2 (20)	0	0.034*	0.001*
Sleep problem	7 (41.2)	5 (23.8)	0.252	4 (40)	0	0.07*	0.001*
Gastrointestinal problem	1 (5.9)	3 (14.3)	0.401	1 (10)	0	0.141	0.02*
Mood swings	4 (23.5)	2 (9.5)	0.239	4 (40)	0	0.002*	0.04*
Dizziness	6 (35.3)	3 (14.3)	0.130	4 (40)	0	0.002*	0.02*
Incontinence	4 (23.5)	1 (4.8)	0.089	3 (30)	0	0.008*	0.05*
Muscle pain	10 (58.8)	6 (28.6)	0.05*	5 (50)	3 (14.3)	0.034*	0.04*
Fatigue	10 (58.8)	5 (23.8)	0.252	4 (40)	0	0.002*	0.01*

Legend: a = intergroup analysis; b = intra-group analysis comparing intervention group at onset and end of study. Fisher's exact test for all analyses; * $p < 0.05$.

Table 5 describes the interventions performed in the IG. A mean of 9.4±1.36 interventions were performed per patient. The mean was 9.8±1.21 among those with episodes of bleeding and 9.2±1.42 (p=0.321) among those with no episodes of bleeding. The following interventions were performed for all patients and are therefore not displayed in the table: I) patient/caregiver counseling on treatment in general; 2) patient/caregiver counseling on specific health conditions and 3) patient/caregiver counseling on overall health. No significant associations were found between the interventions and the occurrence of bleeding during the study period. The recommendation for laboratory exams occurred for all patients with episodes of bleeding and five (45%) were sent to the physician after telephone contact with an indication for an adjustment of the dose. The provision of material (medication organizer) was more frequent for individuals with episodes of bleeding.

Table 5. Pharmaceutical interventions and occurrence of bleeding in intervention group of patients on warfarin in public healthcare system. Ijuí, RS, Brazil, 2019.

Intervention		Bleeding		*p*
		Yes	No	
INFORMATION AND COUNSELING				
Counseling on non-pharmacological measures	*Yes*	10 (55.6)	8 (44.4)	0.462
	No	1 (33.3)	2 (66.7)	
Counseling on self-monitoring	*Yes*	3 (60.0)	2 (40.0)	0.550
	No	8 (50.0)	8 (50.0)	
Counseling on access to medications	*Yes*	6 (46.2)	7 (53.8)	0.392
	No	5 (62.5)	3 (37.5)	
Counseling on storage of medications	*Yes*	8 (53.3)	7 (46.7)	0.633
	No	3 (50.0)	3 (50.0)	
CHANGE OR SUGGESTION FOR CHANGE IN THERAPY				
Suspension of medication	*Yes*	2 (100)	0 (0.0)	0.262
	No	9 (47.4)	10 (52.6)	
Replacement of medication	*Yes*	1 (100)	0 (0.0)	0.524
	No	10 (50.0)	10 (50.0)	
Change of medication dose	*Yes*	1 (50.0)	1 (50.0)	0.738
	No	10 (52.6)	9 (47.4)	
MONITORING				
Recommendation for laboratory monitoring	*Yes*	11 (57.9)	8 (42.1)	0.214
	No	0 (0.0)	2 (100)	
REFERRAL				
Sent to physician	*Yes*	5 (50.0)	5 (50.0)	0.835
	No	6 (54.5)	5 (45.5)	
PROVISION OF MATERIAL				
Medication posology list or calendar	*Yes*	9 (56.2)	7 (43.8)	0.450
	No	2 (40.0)	3 (60.0)	
Pictorial labels/instructions	*Yes*	2 (40.0)	3 (60.0)	0.450
	No	9 (56.2)	7 (43.8)	
Log for self-monitoring	*Yes*	4 (80.0)	1 (20.0)	0.185
	No	7 (43.8)	9 (56.2)	
Medication organizer or device to assist in adherence	*Yes*	4 (66.7)	2 (33.3)	0.367
	No	7 (46.7)	8 (53.3)	

Note: Interventions "sent to nurse, physiotherapist, nutritionist, social support service and structured educational program" were performed for only one patient each, none of whom had episodes of bleeding. Fisher's exact test for all analyses; * $p < 0.05$.

Three patients in the CG and seven in the IG were hospitalized during the study period. No significant association was found between these variables.

In the CG, the mean number of medications among the participants was 7.41±3.14 at the onset of the study and 9.41±3.79 at the end of the study (p=0.004). These figures were respectively 8.00±3.16 and 8.33±3.02 in the IG (p=0.540). The individuals in the CG presented 8.88±5.9 drug interactions at the onset of the study and 10.47±6.87 at the end of the study. These figures were respectively 9.40±5.93 and 9.05±6.37 in the IG. Thus, a significant increase in the occurrence of potential drug interactions occurred in the CG (p=0.002), whereas little change occurred in the IG (p=0.340). The number of drug interactions that increase the risk of bleeding and the number that increase the risk of thrombosis were more frequent in the CG (p=0.044 and p=0.05, respectively).

The main findings of the present study were the smaller number of cases of bleeding in the group that received pharmacotherapeutic follow-up, but with no significant association between these variables. Moreover, no significant association was found between an improvement in TTR and pharmacotherapeutic follow-up. The intervention group had a greater frequency in the therapeutic range for capillary INR but not laboratory INR and with no significant association for either measure. A reduction in thrombotic and other events as well as the minimization of medications and drug interactions were found in the intervention group IG.

Fewer cases of bleeding occurred in the IG but no significant association with follow-up was found. According to the literature, the prevention of bleeding requires educational measures, the promotion of the rational use of medicines, monitoring of the INR and the maintenance of values in the therapeutic range [15], which are similar to the actions performed in the present study. However, some factors may have interfered with achieving more promising results, such as the use of polytherapy, the occurrence of drug interactions, older patients and other factors that were not measured, such as the weekly dose, which is directed related to the occurrence of this event [16].

No association was found between receiving pharmacotherapeutic follow-up and an increase in TTR values in patients in anticoagulation therapy. However, previous studies have found such an association [5, 6, 17]. This divergence may be due to the fact that these studies were conducted in the hospital setting and/or anticoagulation clinics linked to cardiology services, involved multidisciplinary care teams and had larger samples, different follow-up methods and a greater frequency of INR measurements.

One should bear in mind that patients in primary care have difficulty in gaining access to the requisition of INR exam and giving the results to the physician. In one study the majority of patients (73.5%) performed one to five INR exams/year and approximately

half of the patients did not return to the physician to show the results [18]. In the present study, the exams were covered in the research, but the limited budget impeded the execution of a greater number of analyses, which would have been ideal. It should be pointed out that, although monitoring was less frequent in comparison to other studies, it was superior to the frequency of patient analyses in the public healthcare system of the municipality [18].

Warfarin is among the medications most associated with preventable hospitalizations [3]. The number of hospitalizations was greater in the IG than the CG. However, the analysis was not limited only to hospitalizations related to the use of warfarin, which constitutes a limitation of the present study. Moreover, the source of these data were the patients themselves, some of whom were unable to state the reason for hospitalization and this information was not available at the primary care unit.

The occurrence of thrombotic events is less frequent than bleeding but has considerable clinical importance. Cases of thrombosis were more frequent in the CG, but the difference between groups did not achieve statistical significance. Another study achieved the minimization of these events through pharmacotherapeutic follow-up [6]. Risk factors associated with thromboembolic disorders found in the present study included hypertension, smoking, diabetes, dyslipidemia and an advanced age. Thus, the prevention of adverse events involving warfarin should be a priority to ensure patient safety.

Pharmacotherapeutic follow-up minimized drug interactions and reduced the occurrence of adverse events. Most of the patients in the present study were polymedicated and each medication had potential side effects, which underscores the importance of preventive measures and the monitoring of patients exposed to potential interactions. The adverse events addressed in this study may be indirectly associated with warfarin, but other causes cannot be discarded considering the presence of comorbidities, other medications and, consequently, drug interactions. Moreover, the literature reports a greater frequency of warfarin-related adverse events at hospitals [19] as the follow-up of patients is facilitated and more regular in these settings.

The number of interventions performed in the IG was greater among the patients with bleeding, although no significant association was found between the variables. Considering the complexity of warfarin therapy, the high need for interventions and the lack of information found in the present study may be important factors to the increase in adverse events. Thus, the development of counseling strategies is essential.

The adjustment of the warfarin dose was only performed on one patient due to resistance on the part of physicians in primary care. Although the presence of a pharmacist

is a strongly recommended safety strategy in other countries [5] it is not common practice in Brazil.

Regarding the characterization, the results of the present study are similar to those reported in the literature, with a predominance of older people, women and low schooling [4, 20, 21] as well as the indication for the use of an oral anticoagulant [20, 22]. Regarding the duration of warfarin use, a study states that patients starting treatment (less than six months) have more adverse effects and lower TTR values [23]. In the present investigation, time of use ranged from one to 20 years, which may have contributed to the lack of significant differences between groups. It is noteworthy that dropouts were minimal, with some patients in the CG and none in the IG dropping out, which indicates satisfaction with regards to follow-up, as demonstrated in previous studies [24, 25].

The present study has limitations that should be considered. The sample size was too small to enable adequate inferential statistics. Some variables were not controlled, such as adherence to treatment, weekly dose and patient satisfaction with the follow-up. Some information, such as the reason for use and hospitalizations, may not have been reported precisely by the participants. Moreover, the frequencies of the INR tests and visits were pre-established and not based on changes in the exam results.

Conclusion

The intervention by the pharmacist resulted in a reduction in adverse events compared to the control group as well as a reduction in the number of drug interactions. However, no associations were found between pharmacotherapeutic follow-up and bleeding or time in the therapeutic range among patients on warfarin in the public healthcare system.

Although barriers remain regarding the clinical participation of pharmacists in primary care, especially for patients on blood thinners, the present results can help guide future studies with different approaches to these patients. The public health system has frailties and these patients require special attention from the health team. Home care service is accepted well by these patients and can contribute to better care quality.

Disclosure statement

All authors report that they do not have any conflicts of interest.

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