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Evaluation of effect of frailty on warfarin compliance among older patients

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ABSTRACT

Aim: Warfarin has a narrow therapeutic index. We aimed to evaluate the effect of frailty on compliance to warfarin pharmacotherapy and the attainment of international normalized ratio (INR) goals in patients aged over 65 years receiving warfarin.

Material and Method: We recruited 473 elderly subjects aged 65 years and over. Indications for the administration of warfarin and INR values were recorded. All patients were assessed according to the Clinical Frailty Scale of the Canadian Health and Aging Study. Whether or not the target of INR values and the degree of frailty were compared.

Results: Of the 473 patients, 401 patients were assigned to the non-frail group and 72 patients were assigned to the frail group. When patients were compared according to the attainment of target INR values, a negative correlation between frailty and numerical INR values was observed.

Conclusion: It can be said that the presence of frailty negatively affects reaching the target INR values in patients over 65 years of age using warfarin. If patients in this population are indicated for warfarin use, it is necessary to be sure that INR monitoring will be done well.

Keywords: Frailty, geriatric population, warfarin

INTRODUCTION

The American Medical Association refers those with 'frailty' as 'the patient group posing the most complicated and coercive problems for physicians and all health professionals' (1-3). Increased understanding among healthcare professionals regarding frailty in elderly patients may improve the follow-up and management of frail individuals.

A limited number of previous clinical studies have demonstrated that frailty may affect drug compliance in elderly patients (4,5). Warfarin is the most widely used oral anticoagulant in the world. Warfarin, which acts by inhibiting vitamin K epoxide reductase, is used in primary and secondary prevention of thromboembolic diseases. However, studies regarding compliance to treatments such as warfarin requiring a close follow-up are yet to be reported (4,5). Scoring systems commonly used at the initiation of warfarin therapy do not take into account frailty, other than patient age.

In the present study, we aimed to determine the severity of frailty in elderly patients receiving warfarin and to evaluate the relationship between frailty and compliance to pharmacotherapy.

MATERIAL AND METHOD

The study protocol was explained to all participants. Informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and Ethical approval was received from the Health Science University, Ümraniye Training and Research Hospital Ethics Committee, who also approved the study protocol (approval no. 18467, 23.11.12).

In total, 473 patients aged over 65 years who were receiving warfarin treatment for any reason were included in the present study. Exclusion criteria for the study included all patients who did not want to participate in the study, had congenital disability, and had any active diagnosis of malignancy. The medical

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history of all patients was recorded and international normalized ratio (INR) levels were analyzed during three months. The therapeutic INR range was defined as 2.5-3.5. Turkish version of The Criteria of Canada Health and Age Study (CTHAS) were applied to all patients to assess frailty (2). All criteria components were assessed by the same person using a proper and clear tone of voice such that patients were able to fully understand. The degree of frailty was determined according to the ability to walk without assistance, perform activities of daily living without assistance, the presence of urinary incontinence (UI), the presence of stool incontinence (FI), impairment of cognitive function without dementia, the presence of dementia and complete dependence during mobilisation. Patients with only urinary incontinence were considered to be mildly fragile. The need for help in mobility and activities of daily living, cognitive impairment without dementia, and inability to incontinence urine and feces were considered to be moderately to severely fragile.

Statistical Analysis

All statistical analyses were performed using the SPSS 20.0 (Statistical Package for the Social Sciences) IBM Software program. In addition to definitive statistical measures (mean, standard deviation), the Mann–Whitney U test, Kruskal–Wallis test and Spearman's correlation were used to compare non-normally distributed data. The chi-square test was used to compare qualitative data. Statistical significance was assessed at $p<0.05$.

RESULTS

The mean age patients were 71.68±0.23 years (non-frail group), 77.32±0.12 years (mild frail group) and 79.68±0.43 years (moderate/severe frail group). Of all 473 included patients, 263 (55.6%) and 210 (44.4%) were females and males, respectively. Patient characteristics and diagnoses are summarized in **Table 1**.

The severity of frailty was found to be related to walking condition and age. The mean age of patients able to walk unaided was lower than for patients unable to walk unaided. Ability to walk unaided, urinary continence, stool continence, cognitive state, presence of dementia, Daily Life Activity (DLA) and complete dependency in performing DLA were all positively related to patient age **(Table 2).**

A significant relation between the severity of frailty and the attainment of therapeutic INR target was observed in patients with mild frailty or moderate/severe frailty and INR targets <2.5 or 2.5–3.5. A greater relation was observed in patients with target INR >3.5. Whereas 7.3% and 15.3% of patients with moderate/severe frailty failed to attain target INR values of <2.5 or >3.5, respectively, and 2.9% of patients with this degree of frailty did achieve the target INR value. A significant relation was observed between DLA and the attainment of INR targets. The proportion of respondents that reported the ability to perform DLA was higher among patients who achieved INR target values compared to patients with INR values <2.5 or 2.5–3.5. A significant relation was observed between urinary incontinence and the attainment of INR target values. The proportion of respondents with urine incontinence was higher among patients with INR values >3.5 compared to patients with INR values <2.5 or 2.5–3.5. A significant relation was observed between stool incontinence and the attainment of INR target values. The proportion of respondents with stool incontinence was higher among patients with INR values >3.5 compared to patients with INR values <2.5 or 2.5–3.5. A significant relation was observed between dementia and the attainment of INR target values. The proportion of respondents with dementia was higher among patients with INR values >3.5 compared to patients with INR values <2.5 or 2.5–3.5 **(Table 3).**

A significant relationship was observed between the severity of frailty in patients and the achievement of the therapeutic INR target. In patients with increased frailty, the rate of reaching the therapeutic INR value was low. In patients with moderate to severe frailty, only 6 of 31 (19.35%) patients achieved the therapeutic INR. In 41 patients with mild frail, the rate of achieving therapeutic INR was higher with 20 (48.71%) patients than moderate to severe frail patients.

Table 1. Overall patient characteristics and diagnoses

		N	%
Gender	Female	263	55.6%
	Male	210	44.4%
Diagnosis	Atrial fibrillation	299	63.2%
	Valve replacement	112	23.7%
	Deep vein thrombosis	17	3.6%
	Pulmonary embolism	34	7.2%
	Atrial thrombus	6	1.3%
	Cerebrovascular disease	2	0.4%
	Valve + neonatal valve repair	2	0.4%
	Af + atrial thrombus	1	0.2%
Frailty	Normal	401	84.8%
	Frail	72	15.2%
Dla*	No	37	7.8%
	Yes	436	92.2%
Urine	No	453	95.8%
	Yes	20	4.2%
Stool	No	458	96.8%
	Yes	15	3.2%
Cognitive	No	469	99.2%
	Yes	4	0.8%
Dlacomdep**	No	442	93.4%
	Yes	31	6.6%
Dementia	No	459	97.0%
	Yes	14	3.0%
Inr target	On-target	296	62.6%
	Off-target	177	37.4%

*: Daily life activity, **: Complete dependency in performing DLA

Table 2. Comparison of variables according to frailty degree

		Frailty degree						
		Non-frail		Mild		Moderate/severe		P-value†*
		N	%	N	%	N	%	
Walking	No	3	0.7%	41	100%	31	100%	
	Yes	398	99.3%	0	0%	0	0%	<0.001**
Dla§	No	1	0.2%	6	14.6%	30	96.8%	
	Yes	400	99.8%	35	85.4%	1	3.2%	<0.001**
Urine	No	401	100%	37	90.2%	15	48.4%	
	Yes	0	0%	4	9.8%	16	51.6%	<0.001**
Stool	No	400	99.8%	41	100%	17	54.8%	
	Yes	1	0.2%	0	0%	14	45.2%	<0.001**
Cognitive	No	400	99.8%	41	100%	28	90.3%	
	Yes	1	0.2%	0	0%	3	9.7%	<0.001**
Dla-comdep¶	No	400	99.8%	37	90.2%	5	16.1%	
	Yes	1	0.2%	4	9.8%	26	83.9%	<0.001**
Dementia	No	401	100%	41	100%	17	54.8%	
	Yes	0	0%	0	0%	14	45.2%	<0.001**
Sex	Female	224	55.9%	21	51.2%	18	58.1%	
	Male	177	44.1%	20	48.8%	13	41.9%	0.816
Age	Mean±sd	71.68±0.23		77.32±0.12		79.68±0.43		<0.001‡**

*: p< 0.05; **: p< 0.01,
§: daily life activity, ¶: complete dependency in performing dla
†: chi-square test; ‡: kruskal–wallis test

Table 3. Comparison of the variables according to inr groups

		Inr value						
		<2.5		2.5-3.5		>3.5		P-value
		N	%	N	%	N	%	
Frailty	No	164	85.4%	183	87.6%	54	75%	
Degree	Mild	14	7.3%	20	9.5%	7	9.7%	
	Mod/severe	14	7.3%	6	2.9%	11	15.3%	0.0006†**
Walking	No	28	14.6%	28	13.4%	19	26.4%	
	Yes	164	85.4%	181	86.6%	53	73.6%	0.078†
Dla§	No	15	7.8%	11	5.3%	11	15.3%	
	Yes	177	92.2%	198	94.7%	61	84.7%	0.024†*
Urine	No	184	95.8%	209	100%	60	83.3%	
	Yes	8	4.2%	0	0%	12	16.7%	<0.001†**
Stool	No	185	96.4%	209	100%	64	88.9%	
	Yes	7	3.6%	0	0%	8	11.1%	<0.001†**
Cognitive	No	189	98.4%	209	100%	71	98.6%	
	Yes	3	1.6%	0	0%	1	1.4%	0.201
Dlacomdep¶	No	180	93.8%	199	95.2%	63	87.5%	
	Yes	12	6.2%	10	4.8%	9	12.5%	0.072
Dementia	No	189	98.4%	206	98.6%	64	88.9%	
	Yes	3	1.6%	3	1.4%	8	11.1%	<0.001†**
Sex	Female	108	56.2%	113	54.1%	42	58.3%	
	Male	84	43.8%	96	45.9%	30	41.7%	0.79
Age	Mean±sd	72.91±0.45		72.43±0.32		72.9±0.40		0.691##

*: p< 0.05; **: p< 0.01; †: chi-square test; ‡: kruskal–wallis test; §: daily life activity, ¶: complete dependency in performing dla

DISCUSSION

The most important finding of the present study was the observation that the proportion of patients attaining INR target values was lower in frail patients aged over 65 years using warfarin than non-frail patients aged over 65 years using warfarin. Frailty was seen to negatively affect the attainment of INR target values in patients receiving warfarin.

The increasing elderly population has increased the prevalence of age-related diseases, and this makes the concept of frailty an increasingly important clinical issue. A total of 9008 patients aged over 65 years were evaluated in the (CHAS) with the measurements of clinical parameters such as walking without assistance, performance of daily life activities without assistance, urinary and stool incontinence, impairment of cognitive function and dementia used to assess frailty (6). In the present study, the prevalence of frailty was lower than reported in the Cardiovascular Health Study; with the prevalence of frailty determined as 0.7%, 2% and 4% in the 65–74 years age group, 75–84 years age group and the

group aged 85 and over, respectively (6). In the present study, in which the same parameters were used to assess frailty, we found the 15.3% and 9.7% of patients aged over 65 years receiving warfarin had moderate/severe frailty or mild frailty, respectively.

Several previous studies have examined pharmacotherapy compliance in patients aged over 65 years for a number of diseases. Krousel-Wood et al. (7) should that very few elderly individuals were found to comply with pharmacotherapy, with mild and moderate levels of non-compliance observed in a considerable number of patients. Cooney et al. (8) found that drug interactions and antihypertensive drug compliance in elderly patients, the presence of multiple chronic diseases, polypharmacy and decreases in cognitive and functional capacity were all related to decreased compliance.

Numerous factors have been previously reported to negatively affect the attainment of INR target values. Nutrition status, hepatic and renal function, intestinal absorption rate, genetic factors affecting warfarin pharmacokinetics, patient compliance to pharmacotherapy and drug interactions have the greater reported contributions (9). Decreases in K vitamin-dependent factors and increases in warfarin sensitivity necessitate closer follow-up of elderly patients compared to normal patients to attain target INR values. Low doses of warfarin should be used with caution in elderly populations (10).

The relationship between frailty and the attainment of target INR values and factors preventing the attainment of target INR values in geriatric populations receiving warfarin have yet to be fully elucidated. In the present study, we found that frailty negatively affected the attainment of target INR vales in patients aged over 65 years in addition to the negative effects of other clinical parameters such as DLA, dementia, impairment of cognitive activity, urinary and fecal incontinence (FI).

Corroborating the study by Ertas et al. (11) we found age and sex had no effect on the attainment of target INR values.

Compared to patients without dementia or impaired cognitive function, a lower proportion of patients with dementia and/or impaired cognitive function have been shown to attain target INR values (12,13). In the present study, 45.2% of frail patients had dementia. On the other hand, none of the non-frail patients had dementia. In the present study, dementia negatively affected both frailty and the attainment of target INR values.

On the other hand, the proportion of patients able to performed DLA independently was 99.8% in the non-frail group of the present study. However, the proportion of patients able to perform DLA independently decreased to 85.4% and 3.2% in the mild and moderate/severe frailty groups, respectively, with a significant negative correlation observed between DLA independence and frailty. Dependency on others for DLA has a negative effect on the attainment of target INR values.

Previous studies have reported urinary incontinence (UI) as a leading cause of permanent admission to nursing homes (14). Urinary incontinence may preclude individuals from social environments and physical activities and lead to disruptions in DLA, including regular drug use. In the present study, urine incontinence was not observed in any patients in the non-frail group. The proportion of patients with urinary incontinence was found to be 9.8% and 51.6% in the mild and moderate/severe frailty groups, respectively, with a significant relationship between frailty and urinary incontinence observed. In the present study, in which both urinary incontinence and INR targets were evaluated, no patient who achieved target INR had urinary incontinence, whereas the proportions of patients with urinary incontinence patients with INR values below 2.5 and above 3.5 were determined to be 4.2% and 16.7%, respectively. Thus, urine incontinence was found to have a negative effect on the attainment of target INR values.

Although fecal incontinence is not life threatening, it is regarded as an important health problem due to its social, financial, hygienic and emotional pressures on the elder individual in addition to causing significant reductions in the health and quality of life of elderly individuals. No direct studies of the relationship between UI, FI and warfarin compliance have previously been reported. Other studies have demonstrated that UI and FI typically decrease patient quality of life and lead to disruptions in the performance of daily activities. Patients with FI and UI therefore tend to self-administer drugs irregularly leading to decreased pharmacotherapy compliance that further decreases their confidence in treatments and physicians. In the present study, the proportion of patients with FI was 0.2%, 14.6% and 96.8% in non-frail, mild frailty and moderate/severe frailty groups, respectively. A strong relationship was not only observed between frailty and FI, but also between the attainment of target INR and FI. Although no patients who attained INR target values had FI, the proportions of patients with FI in off-target groups with INR values below 2.5 and above 3.5 were 3.6% and 11.1%, respectively. As this result was statistically significant, FI apparently has a negative effect on the attainment of target INR values.

Warfarin and acetylsalicylic acid (ASA) have proven efficacy as first-line treatments for the prevention of stroke and thromboembolic complications. In previous

studies comparing the administration of warfarin with placebo, warfarin was shown to significantly reduce stroke risk compared to placebo. The use of warfarin was unquestionably superior to ASA in preventing chronic atrial fibrillation dependent stroke and thromboembolism (15). Oral anticoagulant treatment with warfarin reduces ischemic stroke risk by 68%, however, it also increases the risk of major concurrent hemorrhagic complications. The proportion of AF patients who do not use warfarin that suffer ischemic stroke in any given year is approximately 12% (16). Hylek et al. (17) reported that 59% of patients have substantial functional disability following AF-related ischaemic stroke. The proportion of patients who do not receive warfarin treatment that develop thromboembolism annually was reported as 2.5 per 100 individuals in the ATRIA cohort, a proportion higher than in other cohorts. Singer et al. (18) reported the high risk of thromboembolism can be reduced with warfarin treatment by 50%. This benefit exceeds the additional risk of warfarin-related intracranial hemorrhage (0.47 per 100 individuals per year with warfarin treatment compared to 0.29 per 100 individuals per year without treatment) (19). Accordingly, the benefits of warfarin use are considered to outweigh the related risks in AF patients (16).

All of these studies indicate warfarin absolutely requires close follow-up. Many studies have shown the failure to attain target INR values can lead to life-threatening complications (9,10). INR values below the target value increase the risk of thromboembolism and values above the target may cause major hemorrhagic complications. In the present study, we assessed frailty in addition to numerous parameters known to affect the attainment of target INR values in elderly patients. As frailty has been shown to have a negative effect on the attainment of target INR values in patients aged over 65 years using warfarin, new generation oral anticoagulants may be considered in such patients.

CONCLUSION

We demonstrated a negative relationship between frailty and the attainment of target INR values, with fewer patients with frailty achieving INR targets. Accordingly, frailty in individuals aged over 65 years apparently has a negative effect on the attainment of target INR values. Therefore, as complications such as embolism and hemorrhage may develop in elderly patients receiving warfarin who are frail or fail to attain target INR values, the close follow-up of such patients should be ensured during warfarin use. Further, we believe that frailty should be included in scoring systems used to assess patients at the initiation of warfarin therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was received from the Health Science University, Ümraniye Training and Research Hospital Ethics Committee, who also approved the study protocol (approval no. 18467, 23.11.12).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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