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Is warfarin usage a risk factor for osteoporotic fractures? A cohort study in the emergency department

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RESEARCH

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ABSTRACT

Background
Several studies have examined the association between warfarin sodium use and risk of osteoporotic fractures with conflicting results. Our study addresses this question, for the first time regarding patients attending emergency department (ED).

Aims
The aim of this study was to retrospectively detect whether there is higher rate of usage of warfarin sodium in patients with osteoporotic fractures attending an ED.

Methods
This is a retrospective study from patients' computerized charts. All individuals >65 years old who had an osteoporotic fracture and attended an ED in a tertiary hospital were compared with a similar group of elderly individuals >65 years old without an osteoporotic fracture who attended the ED for a cause other than an osteoporotic fracture.

Results
This study included 328 patients who were evaluated in the years 2005–2016. Overall, 164 individuals with a typical osteoporotic fracture (hip -66 patients (40 per cent), spine-92 patients (56 per cent), humerus -4 patients (2 per cent), radius -13 patients (8 per cent)) were identified and compared with a matched group of elderly individuals who were evaluated in the ED for other complaints. Warfarin sodium was used in 61 individuals (19 per cent) in the entire cohort, 34 in the fracture group and 27 in the non-fracture group (p=0.324).

Conclusion
In elderly patients, attending an ED, warfarin sodium use does not seem to be a risk factor for an osteoporotic fracture.

Key Words
Warfarin, osteoporosis, fracture

What this study adds:

1. What is known about this subject?
Several studies have examined the association between warfarin sodium use and risk of osteoporotic fractures but the results are conflicting.

2. What new information is offered in this study?
Warfarin sodium is not a risk factor for fracture in elderly patients attending an ED with a new osteoporotic fracture.

3. What are the implications for research, policy, or practice?
The occurrence of an osteoporotic fracture should not

discourage physicians from prescribing warfarin sodium.

Background

Warfarin sodium is a common anticoagulant used for many indications, particularly in the elderly. It is derived from Coumarin, which is a vitamin K antagonist thus preventing the activation of vitamin K-dependant clotting factors.[1-3] Vitamin K plays an important role in bone metabolism as osteocalcin, which enhances calcium binding to the hydroxyapatite bone matrix, contains a gamma-carboxyglutamate group, which may be inhibited by vitamin K.[4-10] Several studies have examined the association between warfarin sodium use and risk of osteoporotic fractures but the results are conflicting.[10-17] Pilon et al conducted a retrospective study on 1523 cases of patients older than 70 and found no statistical association between warfarin use and osteoporotic fractures.[18] The aim of this study was to retrospectively detect whether, as in previous studies, osteoporotic fractures are not associated with the use of warfarin sodium in patients attending an emergency department (ED) with a typical osteoporotic fracture. This is the first study to address this question with an emergency physician perspective.

Method

Rabin medical hospital is a tertiary centre and its ED is the largest in the Middle East, with more than 150,000 annual visits. This retrospective study was performed by review of computerized charts of all independent elderly individuals (>65 years old) who experienced an osteoporotic fracture after minor trauma and attended the ED in the years 2005-2016. An osteoporotic fracture was defined as any one of several typical fractures (femoral neck, vertebra, proximal humerus or distal radius). Those with an osteoporotic fracture were compared with independent gender-matched elderly individuals (>65 years old) attending the same ED but in the internal or surgery wards for reasons other than an osteoporotic fracture.

Patients with fractures not typical of osteoporosis or fractures following major trauma or suspected of being pathologic fractures, patients who used anticoagulants other than warfarin sodium or severely debilitated patients were excluded from the study.

Baseline characteristics (age, performance status, all prescription medications, type of fracture and classification), information regarding treatment with warfarin sodium (dose, effectiveness of treatment-calculated as the percentage of INR measurements within the therapeutic range out of all measurements performed in the previous year- and indication for treatment), information regarding the bone disease (previous fractures, a previous diagnosis of osteoporosis based on results of dual-energy x-ray absorptiometry (DXA) test with T score test <2.5 and treatment for osteoporosis) were compared between the two groups. Use of warfarin sodium in both groups was verified through prescriptions redemptions which were available in the medical records of all those enrolled to the study. This study was approved by the Beilinson hospital IRB.

Statistical analysis:

Sample size calculated to gain a 90 per cent power, considered significant for negative study results, and was 328 patients. The calculation was based on the assumption that there is 10 per cent difference in warfarin consumption between the fracture group and the control group.

Statistical analysis was performed using SAS Software (Version 9.4 of the SAS System for PC, Copyright 2002-2012. SAS Institute Inc). SAS and all other SAS Institute Inc. products or service names are registered trademarks of SAS Institute Inc, Carey, NC, USA. Continuous variables were presented by mean± standard deviation. Categorical variables were presented by N (per cent). T-test was used to compare the value of continuous variables between study groups and chi- square was used to value of categorical variables between study groups. The magnitude of association between continuous variables) was assessed by Pearson correlation.

Results

This retrospective study included 328 patients who were evaluated at Beilinson medical center ED in the years 2005–2016. Overall, 164 individuals with a typical osteoporotic fracture (hip -66 patients(40 per cent), spine- 92 patients(56 per cent), humerus -4 patients (2 per cent), radius -13 patients (8 per cent)) were identified and compared with a matched group of elderly individuals who were evaluated in the ED for other complaints. Baseline characteristics of both groups are presented in Table 1.

Warfarin sodium was used in 61 individuals (19 per cent) in the entire cohort, 34 in the fracture group and 27 in the non-fracture group (p=0.324). The main indication for warfarin sodium usage was atrial fibrillation (44 patients – 72 per cent). In addition, the patients in the fracture group used a higher dose of warfarin sodium compared with the control group (0.79±1.717 *vs.* 0.53±1.415, respectively, P=0.05). Although warfarin sodium was administered for a

longer period of time in the fracture group compared with the control group, the difference was not statistically significant (13.52±34.7 months *vs.* 11.37±34.77 months, p=0.42, respectively) as shown in Table 2.

A higher proportion of individuals in the fracture group had a previous diagnosis of osteoporosis and were treated medically for this indication, but the difference between groups was not statistically significant (60 patients (37 per cent) *vs.* 46 patients (28 per cent), respectively, p=0.125). More patients in the fracture group were treated with bisphosphonates (34 patients (21 per cent) *vs.* 20 patients (12 per cent), respectively, p=0.037) (Table 3).

As noted in Table 2, warfarin sodium was used in 61 individuals (19 per cent) in the entire cohort, 34 in the fracture group and 27 in the non-fracture group, without statistical difference (p=0.324). In addition, there was no association between warfarin sodium use and type of fracture (Table 4).

Discussion

The main results of this study are that warfarin sodium use is not more prevalent in elderly individuals who experience an osteoporotic fracture and this lack of association persists irrespective of duration of treatment, warfarin sodium dose or effectiveness of treatment. There is conflicting evidence in the literature regarding the role of warfarin sodium in inhibiting bone metabolism and its clinical significance. A meta-analysis that examined observational studies, found that warfarin sodium use was associated with a decreased distal radius, but not spine or hip, bone mass.[11] Studies have found an association between an increased risk of fractures in the spine and ribs in women taking warfarin sodium[12] but not with hip fracture in men and women.[13,14] A large study in older women showed that there was no association between the use of warfarin sodium and a decrease in bone mineral density or risk of fracture.[15] In that study, use of warfarin sodium was self-reported. A study by Woo and colleagues revealed that during 3.4 years of follow-up, bone mineral density did not differ significantly between those treated and those untreated with warfarin sodium.[16] On the other hand, another study performed in patients with mechanical heart valves treated with warfarin sodium found that treatment was associated with a decrease in bone mineral density in the spine.[17] Because most studies evaluated bone mineral density and not fracture outcome, the association between actual use of warfarin sodium (not just self-reporting) and osteoporotic fractures is highly debated. Pilon et al., showed no statistical significant association between osteoporotic fractures and warfarin sodium use regarding fracture outcome in elderly patients.[18] This study evaluated the association between established osteoporotic fractures and verified use of warfarin sodium in elderly patients attending an ED, in order to aid the emergency physician to consider the risk factors of the patient to have an osteoporotic fracture. As previous studies evaluated the association between use of warfarin sodium and fractures, this is the first study to evaluate the association between established osteoporotic fractures and warfarin sodium use in ED patients. The lack of association between established osteoporotic fractures and warfarin sodium use supports the fact that warfarin sodium probably does not significantly influence bone morphology and its use should not be considered a risk factor for osteoporotic fractures. This lack of association is in accordance with two recent trails.[19,20] As warfarin sodium is frequently prescribed to elderly individuals who are at risk for osteoporotic fractures, and considering the fact that heparin and low molecular heparin are associated with decreased bone mass,[21] the fact the warfarin use is not associated with fractures is important to a clinician when confronting an ED patient with an osteoporotic fracture.

Limitations

This study has several limitations. First, because data was collected retrospectively and consecutive patients with a diagnosis of osteoporotic fracture were analysed, there is possibly an unpredictable bias; second, the fracture group were slightly older. This may have influenced the rate of use of warfarin sodium between the two groups, although the age difference was small. Third, because we evaluated a cohort of individuals evaluated in the ED, this cohort probably represents the more severe forms of fractures, as less severe fractures were probably treated in clinics outside the ED. It is thus possible that less severe osteoporotic fractures are in fact associated with warfarin sodium use and this study's conclusions should not be generalised to include all osteoporotic fractures. Yet, because fractures evaluated in the ED and particularly hip fractures are the most significant fractures associated with osteoporosis, this lack of association is certainly reassuring. Fourth, there was a difference of gender between the two groups. The reason for this is was the higher prevalence of osteoporosis in female patients. We thought that matching the gender in this case will create a bias on its own when considering a patient attending an ED. Despite all these limitations, the main strengths of this study are the confirmed fractures and actual use of warfarin sodium and the evaluation of INR values in the year prior to the fracture, attesting to the effectiveness of warfarin sodium use.

Conclusion

Warfarin sodium is not associated with osteoporotic fractures in patients attending the ED and the occurrence of an osteoporotic fracture should not discourage the clinician from using warfarin sodium.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

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Table 1: Baseline characteristics of study cohort

Characteristic (N)	Study group N = 164 (%)	Control group N = 164 (%)	P value
Age (mean ± SD)	81.96 ± 8.153	79.63 ± 8.602	0.74 ¥
Gender			0.135 §
Male (%)	52 (32)	98 (60)	
Female (%)	112 (68)	66 (40)	
Previous stroke	39 (24)	43 (26)	0.702 §
Ischemic heart disease	47 (29)	71 (43)	0.08 §
Hypertension	113 (69)	119 (73)	0.544 §
Diabetes mellitus	63 (38)	66 (40)	0.821 §
Fracture location			
Hip	66(40)	0	NA ¶
Vertebral	92(56)	0	NA ¶
Radius	13(8)	0	NA ¶
Humerus	4(2)	0	NA ¶

§ Chi-Square Tests

¥ levene's Test for Equality of Variances

¶ Not available

*Significant value

Table 2: Characteristics of warfarin sodium use in both study and control group

	Study group N = 164 (%)	Control group N = 164 (%)	P value
Warfarin treatment	34 (21)	27 (16)	0.324 §
Warfarin Indication			
Atrial fibrillation	24 (18)	20 (15)	0.51 §
Thromboembolism	6 (5)	3 (2)	0.31 §
Prosthetic valve	0	0	
Other	0	0	
Atrial fibrillation + Thromboembolism	2 (1.5)	4 (3)	0.4 §
Atrial fibrillation + Prosthetic valve	1 (0.5)	0	
Atrial fibrillation + Thromboembolism + Prosthetic valve	1 (0.5)	0	
Warfarin dosage in mg/day (mean±SD)	0.79 ± 1.717	0.53 ± 1.415	0.05*
Treatment duration (mean±SD)	13.52 ± 34.7	11.37 ± 34.77	0.426 ¥
INR ³			
Between 2-3 <10%	2 (6)	3 (12)	0.48 §
Between 2-3 >10%-40%	9 (27)	5 (19)	0.46 §
Between 2-3 >40%	22 (67)	16 (62)	0.9 §
NA ¶	1 (3)	2 (8)	

§ Chi-Square Tests

¥ Levene's Test for Equality of Variances

³ International normalised ratio

¶ Not available

*Significant value

Table 3: prevalence of osteoporosis and relevant medication among cohort patients

	Study group N = 164 (%)	Control group N = 164 (%)	P value
Previous diagnosis of Osteoporosis	60 (37)	46 (28)	0.125§
Osteoporotic treatment			
Bisphosphonates	34 (21)	20 (12)	0.037§*
Raloxifene	3 (2)	0	NA¶
Prolia	1 (0.5)	1 (0.5)	NA¶
Hormone treatment	2 (1)	6 (4)	0.15
Forteo	0	0	NA¶
Protelos	0	0	NA¶
Bisphosphonates + Prolia	2 (1)	1 (0.5)	NA¶
Bisphosphonates + Hormone treatment	1 (0.5)	0	NA¶
Bisphosphonates + Forteo	2 (1)	1 (0.5)	NA¶
Bisphosphonates + Raloxifene	0	1 (0.5)	NA¶

§ Chi-Square Tests

¥ Levene's Test for Equality of Variances

¶ Not available

*Significant value

Table 4: Fracture location and Warfarin treatment in the cohort group

	Study group N = 164 (%)	Control group N = 164 (%)	P value
Warfarin treatment	34 (21)	27 (16)	0.324 §
Fracture location and Warfarin treatment		27/164	
Hip	24442		0.73
Vertebral	22/92		0.14
Radius	41275		0.4
Humorous	42827		0.07

§ Chi-Square Tests