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EFFECTIVENESS STUDY ON LONGITUDINAL LABORATORY MONITORING OF THE INR IN PATIENTS RECEIVING VITAMIN-K ANTAGONIST FOR ATRIAL FIBRILLATION IN R.MACEDONIA

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ABSTRACT

Atrial fibrillation is preventable cause for ischemic stroke and various other thrombo-embolic events. One of the main agents used in the prevention of the consequences are the vitamin-K antagonists. Although efficacy is proven, studies have questioned their efficiency in this setting. Various factors contribute to variations of their efficiency, which is still underinvestigated in many health systems. Few studies have shown varied estimates and cited different reasons for its effectiveness, ranging from subtle differences in diet, concurrent medications use, variable level of enzyme activity to age and compliance of users, which can vary unexpectedly. The aim of the present study of effectiveness is to describe how often patients that use VKA achieve the targeted values for INR. The population consists of the hospital reach area of Clinical Hospital Tetovo, observed for 6 months with routine laboratory investigation for the values of INR. Our study reveals that 57.4% of all measurements of INR where within the target values between 2-3, while 9.7% of all measurements revealed extreme values that can put patients at risk for further thrombo-embolic events or catastrophic hemorrhagic events.

Key words : anticoagulation, time in therapeutic range, coumarins, VKA

INTRODUCTION

Atrial fibrillation is well established risk factor for developing acute ischemic brain stroke, via spontaneous thrombo-embolism in the brain circulation(1,2). This risk factor has been recognized in the past 50 years, leading to 4-fold increased risk when comparing identical populations without atrial fibrillation, although this risk increases with age. The associated health consequences and economic burden of occurrence of acute ischemic stroke in patients with atrial fibrillation are recognized as one of the leading preventable consequences since the advent of anticoagulant therapy(3,4). From the available therapeutic options, such as heparins, vitamin-K antagonists (VKA), direct acting anticoagulants and the new oral anticoagulants(5–8), the VKA agents have been the most utilized, and are the most accessible medicines for the primary and secondary prevention of ischemic brain stroke, due to their cost, generic license and established profile. On the other hand, the coumarin agents have narrow therapeutic range and show wide variation in achieving the desirable effects(7,9–11). The administration of coumarin agents demands regular laboratory monitoring of specific parameters to show and guarantee that the patients have achieved the desirable therapeutic range(12), hence reducing the risk of subdosing, overdosing and other side effects. Despite the demonstrated efficacy(6,13,14), effectiveness studies have shown that in the population of patients receiving

coumarin agents for the same purpose, the laboratory parameters for therapeutic range have been achieved in 45-70% of the patients(15–17). Additionally, studies have shown that up to 15% of the measurements for INR show extreme values, which are well associated with further thromboembolic events on one end (INR < 1.5) or catastrophic hemorrhages on the other end (INR > 4.5) (16,17) .

Aims of the study. The motivation of the present study stems from the problem that no study investigated the local achievement of the desirable laboratory values for the purpose of preventing ischemic brain stroke in patients with atrial fibrillation. Hence, the primary goal of the study is to evaluate the standard laboratory measures for the effect of vitamin-K antagonists in this population at risk, describing the values of INR (with target INR of 2-3) in consecutive measurements and providing estimate for time in therapeutic range, calculated as number in range for INR over total number of measurements. As outcome of interest is achievement of TTR of 60%, because previous findings suggest that values below this threshold are associated with bleeding complications(12).

METHODS AND MATERIAL

The present study is designed as longitudinal study of observation of patients with atrial fibrillation that started with VKA or that were already on VKA, with target range for INR of 2-3. The study is intended to follow patients receiving the therapy for 6 consecutive months. The patient population consists of patients that were registered with new atrial fibrillation or that were already taking VKA from the hospital registry in the Clinical Hospital – Tetovo. The patients were recruited from the period of 01/01/2019 to 01/03/2019, with planned end of the study follow-up of 01/09/2019. Although the recruitment time was only two months, it allowed that the patients can be followed up within the same time frame, which can evade erroneous errors due to seasonal variation in diet (vegetables that contain Vitamin-K) and lead to confounding(18).

For inclusion of the study, the diagnosis of atrial fibrillation was confirmed with 12-lead ECG recording done in the past 30 days or at the moment of initiation in the study, confirmed by trained cardiologist. The target INR for this indication is set to values between 2 and 3. As excluding criteria for the study are known presence of biological or mitral valves, pacemaker, past deep venous thrombosis, recent pelvic operations and other conditions which demand different targets for INR. All patients left data on their age, gender and presence of the following comorbidities – past brain stroke, myocardial infarction, previous operative procedures or intervention regarding the heart, past deep vein thrombosis. Besides anamnestic data, the hospital records of the patients were also checked for the fore-mentioned conditions and presence of any of the exclusion criteria.

Use of VKA therapy. Acenocoumarol(7) (4mg, tablets) is the only registered and publically available VKA in Macedonia, and hence the studied drug in the study. All patients started receiving VKA or were already using VKA therapy for the described purpose. All patients that started with VKA in this study were followed with laboratory measurements for titration of therapy(6), and those measures are excluded from the analysis. The laboratory measurement that ensures that the patient has achieved the target of the therapy is the international standardized ratio (INR)(19,20). The blood samples of the patients were collected during routine check-ups at the Transfusiology Unit as part of the Clinical Hospital – Tetovo on a monthly basis. The INR represents a ratio between patient's prothrombin time (PT) and the normal values for PT, determined by the local laboratory; the resulting ratio is then exponentiated by a specific number called international sensitivity index (ISI) (21), which corrects for the use of different thromboplastins that are used for the determination of INR, hence producing standardized results. The formula for calculation of INR is ISI .

Besides the standard measurement of INR, our Transfusiology Unit makes routine measurements of other parameters, such as thrombocyte count, and were examined by trained transfusiologist for extreme values, laboratory errors and handling of the specimens.

Follow-up of laboratory values for INR. All included patients were instructed to make monthly measurements of INR at our Clinic, as part of the standard practice. For the observation period of 6 months, it is anticipated to generate 7 measurements of INR per patient, as the usual local practice for this indication is to monitor INR on monthly basis. Of interest are the values for the measured INR and extreme findings. The values for extreme findings are the values below or above which best predict risk for ischemic complications and brain hemorrhage, respectively. So far, values of INR above 4.5(22) increase the risk for bleeding event 4.6 times in

comparison with INR values below. For threshold for risk for new thrombo-embolisms, we used value for INR below 1.5. For the calculation of the summary measure for achieving the target INR, two approaches are available(15). First, one can calculate the proportion of values for INR that lie between 2 and 3 and divide with the total number of measurements, irrespective of the patients. The advantage is that this approaches provides gross estimate, regardless of missing data or loss due to follow-up. In asymptotic conditions, this estimator can be approximated by the normal distribution. The second approach is to estimate the time in therapeutic range for each patient, which is achieved by including the number of measurements for INR in the desired interval over the total number of measurements for each patient. This approach provides estimate on the laboratory measures of INR values for each patient. Due to expected loss of patients due attrition, it is anticipated that this approach cannot provide an estimate for each patient included in the study. Second, as this approach is used to estimate the fulfillment of time in therapeutic range above 60%, only data from patients that made at least 4 measurements are included in this analysis.

Statistical analysis. The software of choice for the present analysis is IBM SPSS v24(23). The first part is providing descriptive data on the patient's demographic characteristics, such as age, gender, ethnicity, previous use of VKA, presence of arterial hypertension, presence of diabetes mellitus and past cerebrovascular insults, as mean with SD or proportion, whichever suits the type of the variable.

The summary measures for the values of INR are going to be described with mean, SD, 95% CI. Number of measurements with extreme values for INR (<1.5 or >4.5) and measurements that are not in therapeutic range (<2 and >3) are going to be examined. Time in therapeutic range is going to be calculated as described in the methods section, providing gross estimate and patient estimate on the desired TTR of at least 60%.

RESULTS

Patient characteristics - From 165 potential patients drawn from the registry of our hospital, 128 (77.5%) patients were recruited. The mean age of the patients was 64.4 years, with SD of 6.57. From 128 patients, 72 patients were male (56.3%), while 56 patients were female (43.8%). From the total number of patients, 39 (30.5%) patients were patients were VKA was started, while 89 (69.5%) were patients already taking VKA. From the 128 patients, 96 patients showed on the concluding visit 6 months afterwards. All of the demographic characteristics of the patients are available in table 1. Regarding the number of drop-outs in the observation period, from total 32 patients, 20 patients stopped using the medication due to other medical indication (3 patients with thrombocytopenia, 7 patients with planned operative procedures, 3 patients switched to new oral anticoagulants, while no data was available on 7 patients), while for the remaining 12 patients, 8 patients changed the place of living, while data was unavailable for 4 patients.

Measuring of INR – Values for INR are obtained in 695 (77.6%) measurements. From the patients that were lost during follow-up (32 patients), 102 measurements were made, resulting in average value of 3.2 measurements per patient lost to follow up. Since this number is insufficient to produce TTR, their data is excluded from calculating the outcome parameter – time in therapeutic range (TTR). The mean values and the SD of all measurements of INR per visit are available in table 2. The grand mean of all laboratory measurements was 2.3. The data was checked for normality assumption, by using the Smirnov-Kolmogorov test for normality of data, with the conclusion that the data does not deviate from normality (p-values are presented in the same table).

Table 1 – Demographic characteristic of the enrolled patients and the patients that finished the study.

	Enrolled patients (n = 128)	Patients that finished the study (n = 96)
Age (x, SD)	64.38 (6.57)	64.9 (6.4)
Gender (%)		
Male	72 (56.3%)	50 (52.1%)
Female	56 (43.8%)	46 (47.9%)
Use of VKA		
New patients	39 (30.5%)	29 (30.2%)
Patients already taking VKA	89 (69.5%)	67 (69.8%)
Ethnicity		
Macedonian	36 (28.1%)	26 (27.1%)
Albanian	62 (48.4%)	48 (50%)
Other	30 (23.4%)	22 (22.9%)
Presence of diabetes mellitus or use of oral antidiabetic drugs/ insulin		
Yes	39 (30.5%)	26 (27.1%)
No	89 (69.5%)	70 (72.9%)
Presence of arterial hypertension/use of drugs for arterial hypertension		
Yes	92 (71.9%)	70 (72.9%)
No	36 (28.1%)	26 (27.1%)

The proportion of values that were in the therapeutic range for INR per visit are plotted on image 1. The summary data on extreme values defined as values for INR bellow 1.5 or above 4.5 are presented in table 3. Our group of patients revealed that out of 695 measurements, 48 (6.9%) of the values were below 1.5 or above 4.5, indicating increased risk for embolic event / haemorrhagic event. From 48 measurements, 47 were bellows 1.5 (6.7 % of all measurements), while 27 (3.8%) were above 4.5.

Table 2 - Descriptive estimates for the INR values obtained in 7 measurements

INR measurement	1	2	3	4	5	6	7
Missing measurements	0 (0)	17 (21)	10 (17)	13 (16)	14 (20)	15 (21)	14 (23)
Average values	2.13 (2.11)	2.79 (2.81)	2.34 (2.32)	2.45 (2.46)	2.14 (2.10)	2.21 (2.21)	2.1 (2.06)
Standard deviations	0.49 (0.49)	0.52 (0.48)	0.41 (0.41)	0.43 (0.41)	0.32 (0.34)	0.52 (0.53)	0.45 (0.44)
Kolmogorov-Smirnov statistic	0.084 (0.049)	0.086 (0.067)	0.078 (0.069)	0.064 (0.075)	0.077 (0.075)	0.077 (0.073)	0.72 (0.061)
p-value	0.15 (>0.2)	>0.2 (>0.2)	>0.2 (>0.2)	>0.2 (0.133)	>0.2 (0.174)	>0.2 (0.196)	>0.2 (>0.2)

* Numbers inside brackets are derived from all enrolled patients (n=128)

Table 3. Proportion of measurements in extreme, sub-therapeutic and therapeutic range.

	Data from all measurements (n = 695)	Measurements from patients that finished the observation period (n = 593)
INR < 1.5	48 (6.9%)	34 (5.7%)
INR < 2.0	207 (29.7%)	153 (25.8%)
INR > 3.0	89 (12.8%)	50 (8.43%)
INR > 4.5	27 (3.8%)	14 (2.3%)
INR 2-3	399 (57.4%)	390 (65.7%)

Overall, the mean value for achieving therapeutic range was 0.64 (95% 0.34 – 0.94), while 67 (69.8%) of the patients had TTR of above 60%. Out of 96 patients, only 3 patients had TTR of 1 (all measurements of INR within range), while 21.9% of the patients had TTR below 0.5.

In order to examine possible relationship between achieving TTR above 60% and age, independent sample-t test was conducted, resulting with statistically insignificant result. The association between gender and TTR>60% yielded statistical independence using the Pearson's chi-square test, with value of 0.159 and both-sided asymptotic significance of 0.690.

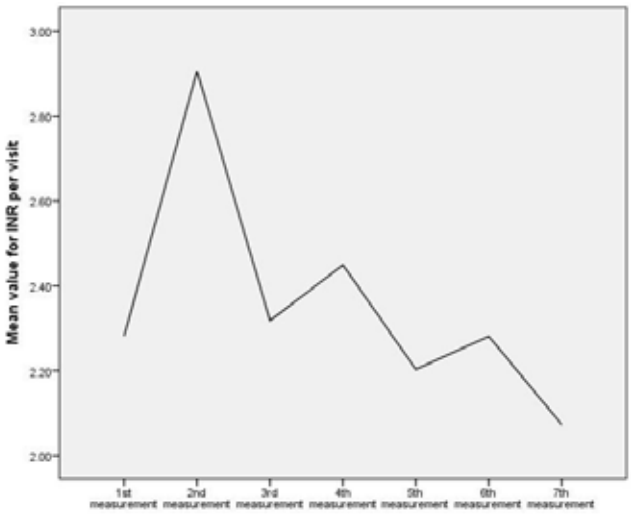

Image 1 – Plot of average values of INR for each measurement

DISCUSSION

Our results show that almost 70% of the patients that were followed for 6 months were in therapeutic range for INR at least to 60% of the measurements. This result is also in line with the findings that patients recruited in randomized control trials have fairly high time in therapeutic range, while in real time conditions this is not achieved(24). Although few studies have reported lower values for TTR, this can be partially explained by the fact that certain populations (countries in the geographical East for instance typically report that majority of patients achieve TTR less than 50%(25,26)) have different diets (hence variations in Vitamin K in food) and different prevalence of important polymorphisms for epoxide oxidase for Vitamin K (which intensifies the anticoagulant effect of VKA, leading to higher number of haemorrhagic events). The same goes both ways – populations that use VKA and have lower number of such polymorphisms, achieve better TTR, for instance Europe. The lack of association of TTR and age and gender in our study could be indicative that the observation period was small to detect such differences(27). For instance, most of the studies that examined TTR and report gender differences have observed the patients for longer (at least 1 year)(27,28). The association between older age and higher TTR has been reported from larger studies as significant, while in our study the mean age of the patients that achieved TTR>60% was insignificantly larger from the other group, with difference of 1.6 years.

Regarding the number of patients that are not in therapeutic range, more patients had values below 2 than

values above 3, which is in line with results from other population cohorts.(28) Extreme values were observed in 6.9% (<1.5) and 3.8% (>4.5) of all measurements, which is close to estimates from other studies. This finding reflects probably a conservative approach in dosing, but it cannot be ruled out that patients consumed food rich with Vitamin-K.

From all recruited 128 patients, there were 32 drop-outs. Although 10 patients reported change of place of living and 12 patients stopped using VKA due to other medical indication, data was unavailable on 10 patients, which does not rule out that they have experienced a side effect of the VKA. This indicates possibility for bias that overestimates the main measurements of the study.

In summary, our study observed that extreme values for INR in anticoagulated patients with AF are common, and necessitate further investigation on how many patients actually experience outcomes related to hemorrhagic events and thromboembolic events.

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