Role of TCD emboli-monitoring in evaluation of efficacy of anti-coagulant therapy in patients with nonvalvular atrial fibrillation

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Abstract

Atrial fibrillation (AF) is a risk factor for stroke but, despite anticoagulation therapy, the risk of stroke is not completely eliminated. We evaluated the presence of microembolic signals (MES) by TCD emboli-monitoring in AF patients receiving various anticoagulation therapies.

In total, 103 patients were divided into four therapeutic groups (receiving warfarin, dabigatran, rivaroxaban, or apixaban; 22 patients in each group) and a control group (15 patients). Common stroke risk factors were evaluated, such as arterial hypertension, ischemic heart disease, history of TIA/stroke, diabetes mellitus, and hyperlipidemia. TCD emboli-monitoring was performed on bilateral middle cerebral arteries for 45-60 minutes.

No statistically significant differences were determined regarding the presence of risk factors between all groups. We found 2 MES in the warfarin group, 1 in the rivaroxaban group, 4 in the dabigatran group, and 0 in the apixaban group. One patient had positive MES in the control group. No statistical differences were seen when the groups were compared with the control group or with each other.

TCD emboli-monitoring can be used for MES detection in patients with AF receiving anticoagulation therapy and thus for the identification of patients at high risk of stroke occurrence/reoccurence.

Keywords: emboli-monitoring, atrial fibrillation, stroke prevention, TCD

Introduction

Atrial fibrillation (AF) is a well–known independent risk factor for ischemic stroke. Approximately 70% patients with AF are 65–85 years old (1). Untreated AF increases the risk of stroke by five-fold (2,3,4). Risk of stroke in AF patient increases with age and other risk factors. Antiplatelet therapy is not effective in primary and secondary stroke prevention in patients with AF. Preventive therapies of choice include oral anticoagulants such as warfarin, dabigatran etexylate, apixaban, rivaroxaban, and edoxaban. These drugs significantly reduce the risk of stroke in the

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patients with AF. However, clinical trials of the novel anticoagulants suggest that, each year, 10–20% of individuals with AF suffer a stroke (5,6,7). Hence, medication significantly reduces the risk of stroke but does not eliminate it completely. Several possible reasons can be proposed as to why such anticoagulant therapy is not effective. The nonclompliace of the patient might be the most important factor and should be considered initially. Other factors are the underdosing of patients, genetic resistance, and, especially in the case of warfarin, food interactions. Other important reasons of stroke reccurence might be different stroke ethiologies (i.e. aterothrombosis). The identification of non-responders of anticoagulants is important, because these patients are at high risk of stroke reccurence and need special attention. Several methods are available regarding the identification of non-responders. The worst scenario is clinical identification, when a patient presents with a new stroke. Non-responders can be also identified radiologically, whereby new asymptomatic stroke is found incidentally during CT or MRI. Routine monitoring of the anticoagulation activity of novel anticoagulants is not recommended, although it is probably the best way of evaluating its effectivenes. In the case of warfarin, regular INR monitoring is needed. The efficacy of rivaroxaban, apixaban, and edoxaban can be monitored via anti-factor Xa activity evaluation. Dabigatran etexylate activity can be monitored by aPTT or, when a more precise evaluation is needed, by the ecarin clotting time (ECT).

These methods are complicated and expensive. We present here the results of our study in which transcranial ultrasound embolimonitoring was used to detect microembolic signals in patients with nonvalvular AF treated with oral anticoagulation therapy.

Aims

The aim of our study was to determine whether positive microembolic signals (MES) occurred during TCD embolic monitoring in patients who suffered from nonvalvular AF and who were also clinically stable on oral anticoagulation therapy. We further wish to compare the presence of MES in various groups of patients and to detect possible risk factors influencing the presence of MES.

Material and methods

Patients with nonvalular symptomatic, asymptomatic permanent or paroxysmal AF were enrolled in the prospective clinical study during the years 2015- 2017. Patients were divided into four groups according anticoagulation type: the warfarin, rivaroxaban, dabigatran (110 mg or 160 mg), or apixaban groups. The control group consisted of patients of similar age, gender, and comorbidities but without anticoagulation therapy. Patients in the anticoagulation groups had to be stable on therapy for at least 1 month. Comorbidities such as arterial hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemy, previous TIA, or stroke were noted for all patients.

The RIMED Digi-Lite™ Digital Transcranial Doppler (TCD) System with an advanced and proprietary M-Mode display and 2 channel bilateral emboli-monitoring with 2 MHz probes was used. Patients were monitored for 40-60 min. The middle cerebral artery (MCA) on both sides were manually identified at a depth of 50-55 mm. For emboli detection purposes, measurements were carried out simultaneously at two depths of same MCA wtih a 5-mm difference. Fast Fourier transformation with 256 points was used. Other settings were as follows: filter 100 Hz, 100 % power, and 6 kHZ pulse frequency. The MES intensity level was set to 9 dB and above. Automatic MES multigate detection was followed with manual control of all patients during data post-processing. MES or artifacts were identified according to the International Consensus Group on Microembolus Detection. The criteria were: duration less than 3 ms, typical acoustic characteristics, random distribution during cardiac cycle, acustic intensity of 9 or more dB above background noise, and unidirectional signal. All data were digitally

recorded for further analysis. As a positive finding, we considered at least one MES registered during a session.

The Pearson Chi square test with the Yates correction was used for the statistical analysis of data.

This study was approved by the local ethical committee, and all participants signed an informed consent form.

Results

In our prospective study, 103 patients were evaluated, with 22 patients being included in each of the four therapeutic groups (warfarin, rivaroxaban, apixaban, and dabigatran) and 15 patients in the control group [48 males and 55 females, with a median age of 72 years (43-89)]. Of the patients, 35 had paroxysmal AF and 55 permanent AF.

The incidence of seleced comorbidities, such are arterial hypertension, ischemic heart disease, diabetes mellius, hyperlipidemia, and history of TIA/stroke, in the study population are shown in table 1. We were found no statistically significant differences between the treatment groups or control group.

From all the subjects, 8 patients (7,7 %) had a positive MES finding during emboli-monitoring: 2 patients in the warfarin group, 4 patients in the dabigatran group (2 patients using160 mg and 2 patients using110 mg dabigatran), 1 patient in the rivaroxaban group, and 1 patient in the control group. No MES were found in the apixaban group. One patient with a positive MES finding in the control group had AF and was treated only with antiplatelet (clopidogrel) therapy. The Chi square test showed no significant difference in the presence of MES, when all groups were compared. We did not find a significant influence of the risk factors on the presence of MES.

Discussion

We have found positive MES in all groups except for the apixaban group. Demir et al. (8) published results of a clinical study in which the MES incidence was 32 (32%) for warfarin, 24 (36%) for rivaroxaban, and 17 (35%) for dabigatran. Apixaban was not evaluated. No statistically significant differences were seen in the incidences of MES when all groups were compared. Our results are similar, although we have determined a lower incidence of MES (from 0 % for apixaban to 18% for

Table 1. Study population characteristics, risk factors, type of AF, and presence of MES

Risk factors	**warfarin n=22**	**rivaroxaban n=22**	**apixaban n=22**	**dabigatran n=22**	**control n=15**
Arterial hypertension	21	20	20	22	14
Ischemic heart disease	19	17	21	21	12
Hyperlipidemia	6	7	5	8	5
TIA/Stroke	4	7	9	4	1
Diabetes mellitus	2	4	5	2	2
Type of AF					
Permanent fibrillation	15	15	11	14	1
Paroxysmal fibrillation	7	7	11	8	1
MES	**2**	**1**	**0**	**2/2**	**1**

dabigatran). The lower frequency of MES might be the result of statistical error because of the smaller population in our study. All subgroups of patients have a comparable presence of risk factors (arterial hypertension, TIA/stroke, diabetes mellitus, and ischeamic heart disease).

The detection of MES might be an important marker of inadequate anticoagulation activity. TCD emboli-monitoring is a relatively simple and cheap diagnostic method for the identification of AF patients who, despite receiving anticoagulation therapy, are at a high risk of stroke. The therapeutic strategy in the patients with a positive MES finding is problematic. The best method is probably to change the anticoagulation therapy, followed by renewed TCD emboli-monitoring. A point worth stressing is that carotid artery disease is a risk factor for positive MES (9), and so this pathology has to be excluded before any decision can be made regarding therapy change.

Resumo

Atria fibrilacio (AF) estas riskfaktoro por apopleksio, sed malgraŭ antikoagulanta terapio, la risko de apopleksio ne estas tute forigita. Ni taksis la ĉeeston de mikroembolaj signaloj (MES) per TCD-embolomonitorado en AF-pacientoj ricevantaj diversajn antikoagulantajn terapiojn. Entute, 103 pacientoj estis dividitaj je kvar terapiaj grupoj (ricevante warfarinon, dabigatranon, rivaroksabanon, aŭ apiksabanon; 22 pacientoj en ĉiu grupo) kaj kontrolgrupo (de 15 pacientoj). Oni taksis komunajn riskfaktorojn, kiel ekzemple arterian hipertension, iskemian kormalsanon, historion de TIA / apopleksio, diabeto kaj hiperlipidemio. TCD embolo-monitorado estis farita je la mezaj cerebraj arterioj ambaŭflanke dum 45-60 minutoj. Ne statistike signifaj diferencoj estis determinitaj koncerne la ĉeeston de riskfaktoroj inter ĉiuj grupoj. Ni trovis 2 MES en la warfarino-grupo, 1 en la grupo kun rivaroksabano, 4 en la dabigatrano-grupo, kaj 0 en la apiksabano grupo. Unu paciento havis pozitivan MES en la kontrolgrupo. Neniu statistika diferenco estis vidita kiam la grupoj estis komparitaj kun la kontrolgrupo aŭ kun la aliaj. TCD embolo-monitorado povas esti uzata por MES-malkovro ĉe pacientoj kun AF ricevantaj antikoagulantan terapion kaj tiel por identigo de pacientoj kun alta risko de apopleksio/recidivo.

Ethics

This study was approved by local Ethical Committee of the Jessenius Faculty of Medicine in Martin, Comenius University. Authors declarated no conflict of interest.

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