Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Ischemic Stroke and Atrial Fibrillation Who Concurrently Take Antiepileptic Drugs

Kanvara Chaibenjapol, Juthathip Suphanklang, Pornwalai Boonmuang, Chesda Udommongkol

Abstract

Background: Most antiepileptic drugs (AEDs) were contraindicated in co-administration with NOACs because of potential interactions that may cause an increased risk of bleeding or reduced antithrombotic efficacy. Epileptic seizures following ischemic stroke are common. So far, there was limited evidence of NOACs and clinical outcomes in patients who concurrently use AEDs.

Objectives: The study aims to compare both efficacy and safety outcomes in stroke patients who required NOACs with AEDs with patients who on NOACs alone. Recurrent rates of ischemic stroke and bleeding during 1-year period are the clinical outcomes.

Materials and Methods: A retrospective cohort clinical study was conducted at Phramongkutklao hospital between January 2016 to January 2021. Patients with AF and history of ischemic stroke who on NOACs for secondary prevention were enrolled and assigned into concomitant AEDs group and no AEDs exposure group (control). The incidence of recurrent ischemic stroke and bleedings during the 1-year period were recorded by review the medical records.

Results: A total of 186 eligible patients were enrolled. 94 patients were assigned into concomitant AEDs group and 92 patients were assigned into no AEDs exposure group (control). The incidence of recurrent ischemic stroke within one year was higher in the no AEDs group, however there was no statistically significance between both groups (5 cases vs. 2 cases, OR=2.53, 95% CI, 0.48 to 13.37; *p=0.44*). For safety outcome, there were 11 events of minor bleeding in the AEDs group and 4 events in the no AEDs group but there was no

Kanvara Chaibenjapol[1], Juthathip Suphanklang[2], Pornwalai Boonmuang[2], Chesda Udommongkol[3]
[1]3rd year Neurology Resident, Phramongkutklao Hospital
[2]Department of Pharmacy, Silpakorn University
[3]Department of Medicine, Phramongkutklao Hospital

Corresponding author:
Kanvara Chaibenjapol
3rd year Neurology Resident, Phramongkutklao Hospital, Bangkok, 10400 Thailand
E-mail : ployrolliez7@gmail.com

statistically significant difference in any bleeding between groups (OR=2.92, 95% CI, 0.89-9.52; *p=.10*).

Conclusion: The incidence of recurrent ischemic stroke and bleeding were not significantly different in AF patient who take NOACs concomitant with AEDs and NOACs alone group. So, it may be reasonable to safely use AEDs with NOACs to treat epilepsy in patient with stroke.

Keywords: Non-vitamin K antagonists, Antiepileptic drugs, recurrent stroke, bleeding, drug-drug interactions, NOACs plasma level

Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) including dabigatran, rivaroxaban, apixaban and edoxaban have been extensively prescribed in Thailand for stroke prevention in patients with atrial fibrillation (AF) in the absence of a mechanical prosthetic heart valve or without moderate to severe mitral stenosis.[1] NOACs are systematically considered to be associated with non-inferiority[2-4] or somehow superior[5] to Vitamin K Antagonist (VKA) in prevention of stroke and systemic embolism in AF patients. Moreover, NOACs cause significantly lower major bleeding risk than the VKA. In addition, NOACs show improved efficacy to safety ratio and fewer food and drug interactions comparing with VKA. Regarding the EHRA 2018 practical guideline on NOACs, most antiepileptic drugs (AEDs) were contraindicated in co-administration with NOACs because of potential interactions.[6] This combination may cause an increased risk of bleeding or a reduced antithrombotic efficacy.[7] The majority of pharmacokinetic interactions are mediated by metabolism via CYP3A4 and P-Glycoprotein (P-gp). Accordingly, both first and second generation AEDs with CYP3A4 or P-gp inducer or inhibitor properties, for examples; Phenytoin, Valproic acid, Carbamazepine, Phenobarbital, Topiramate and Levetiracetam, are warningly contraindicated and carefully avoided.

In fact, epileptic seizures following ischemic stroke are common, and AEDs are routinely recommended.[8] Therefore, the use of plasma level monitoring for NOACs dose-adjustment may be safe and helpful in prescribing the combination regimens. However, there was limited evidence, so far, about NOACs plasma levels in patients who concurrently use antiepileptic drugs. Hence, this research was designed to monitor both efficacy and safety outcomes in stroke survivors who required NOACs with AEDs comparing to cases who only on NOACs without AEDs. The clinical efficacy will be focused on rates of recurrent ischemic stroke and safety outcomes are bleeding during the 1-year period of using both NOACs and AEDs.

Objectives

1. To evaluate recurrent ischemic stroke events for clinical efficacy outcomes of NOACs in patients who concurrently take NOACs and AEDs
2. To evaluate bleeding events for clinical safety outcomes of NOACs in patients who concurrently take NOACs and AEDs

Materials and Methods

Study design

This retrospective cohort clinical study was conducted in stroke center and neurology division at Phramongkutklao hospital between January 2016 to January 2021. This project was approved by the Institutional Review Board Royal Thai Army Medical Department: R108h/63.

Trial Population

Patients with AF and a history of ischemic stroke who on NOACs for secondary stroke prevention were enrolled. Eligible cases must continuously take NOACs for at least 1 year concomitantly with AEDs for any indications including epilepsy, mood disorder or neuropathic pain. In case of seizures, the seizure must be well controlled. The study excluded patients with severe kidney disease (CrCl < 15 ml/min), liver disease (Child-Pugh Class C) and patients who on known drugs that may potentially interact with NOACs. Controls were patients with AF who took NOACs for secondary prevention without AEDs. Dosages of NOACs must remain unchanged for at least 7 days before recruitment in the laboratory test.

Procedures

Recruited patients who currently on NOACs were assigned into concomitant AEDs group and no AEDs exposure or control group. Demographic data and comorbidities were reviewed and recorded. Type of NOACs, dosages and time were also noted. Latest CrCl within 3 months prior the registry were also recorded. The clinical outcome of the incidence of recurrent ischemic stroke and any bleeding events were collected by review the medical records and diagnostic imagings.

Outcomes

The primary outcomes were the incidence of recurrent ischemic stroke and bleeding events within medication exposure period of 12 months.

Outcome definitions

Bleeding events referred to any bleeding occurrence in patients who took NOACs with or without AEDs within 12 months, based on the definition of bleeding on International Society on Thrombosis and Hemostasis (ISTH).

- Major bleedings: fatal bleeding and/or symptomatic bleeding in critical organ, such as intracranial, intraspinal or retroperitoneal and/or bleeding causing a fall of Hb level of 2 g/dl or more, or leading to transfusion of two or more units of whole blood or red cells.
- Minor bleedings: other bleeding out of the criteria for major bleeding

Recurrent ischemic stroke referred to occurrence of ischemic stroke or transient ischemic attack (TIA) during taking NOACs for secondary stroke prevention within 12 months. These outcomes were diagnosed and reconfirmed by neurologists.

Statistical Methods

Statistical analysis was evaluated by using SPSS 27.0 statistical software. Descriptive statistics were used in demographic data. Continuous data were described in mean, SD. Comparison of the difference between groups was made by paired t-test or Mann-Whitney U test. Discrete data was described in percentage and were analyzed by Chi-square or Fischer-exact test.

Results

From January 2016 to January 2021, a total of 186 eligible patients were enrolled. 94 patients were assigned into NOACs exposure with AEDs group and 92 patients were assigned into without AEDs exposure or control group. The baseline characteristics of all patients were shown in Table 1. The mean age was 75 years, and 57% of cases were men. The most common NOACs use in coexisting AEDs group was Dabigatran (29%) and Pregabalin is the most concomitant AEDs used with NOACs.

For primary outcome, the incidence of recurrent ischemic stroke within one year was higher in the

no AEDs group, however there was no statistically significance between the with AEDs and without AEDs group (5 cases vs. 2 cases, OR=2.53, 95% CI, 0.48 to 13.37; *p=0.44*). For safety outcome, bleeding events were inversely more frequently observed in the AEDs group. There were 11 events of minor bleeding in the AEDs group and 4 events in the no AEDs group (OR=2.92, 95% CI, 0.89-9.52; *p=.10*). In contrast, major bleeding was not found in AEDs group but those were observed in 2 cases including gross hematuria and bleeding rectal ulcer in no AEDs group. Ultimately, there was no statistically significant difference in major bleeding, minor bleeding and any bleeding as shown in Table 2.

Discussion

In this study, the aims were to demonstrate efficacy and safety of NOACs following the recommendation from The EHRA 2018 using NOACs guideline that several AEDs are contraindicated in concurrently use with NOACs. As some AEDs (levetiracetam, phenobarbital, phenytoin, carbamazepine, oxcarbazepine and topiramate) may reduce the NOAC plasma levels which may lead to embolic phenomena, so they are contraindicated or use with caution (oxcarbazepine and topiramate) for combination with NOACs.[1] Whereas some AEDs may increase NOACs plasma levels that may lead to bleeding complication. From these hypotheses, patients with a history of ischemic stroke with AF who took NOACs as secondary prevention in concomitant with AEDs in any indications, the incidence of recurrent ischemic stroke should trend to be higher than patients who take NOACs alone. However, this study did not show significant difference of ischemic stroke recurrent rates between 2 groups. For safety concern, the incidence of bleeding events were not significantly different between with AEDs vs. without AEDs groups. In contrast to previous publications, Risselada reported events of pulmonary embolism developing after concomitant use of rivaroxaban 10 mg QD as thromboprophylaxis with carbamazepine, a CYP3A4 inducer.[9] In 2020, Wang CL also published that the concurrent use of NOACs and valproic acid, phenytoin, or levetiracetam was significantly associated with a higher risk of major bleeding.[10] Nevertheless the results from this study may support more optional treatment of post stroke epilepsy in Thai patients in the real practical situation regarding efficacy and safety of NOACs, although some AEDs including lamotrigine, gabapentin, pregabalin and zonisamide were not warned in the recent recommendation.

Conclusion

The incidence of recurrent ischemic stroke and bleeding were not significantly different in AF patient who take NOACs concomitant with AEDs and NOACs alone group. So, it may be reasonable to safely use AEDs with NOACs to treat epilepsy in patient with stroke.

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