Antithrombotic Treatment Prior to Intracerebral Hemorrhage: Analysis in the National Acute Stroke Israeli Registry

Roy Romem, BSc,* David Tanne, MD,* Diklah Geva, PhD,† Michal Einhorn-Cohen, BSc,† Nir Shlomo, MSc,† Sara Bar-Yehuda, PhD,† and Sagi Harnof, MD*,§

Background and Purpose: Intracerebral hemorrhage (ICH) is the most disastrous stroke subtype. Prognosis is considered worse with prior antithrombotic treatment. Our aim was to evaluate the association of prior antithrombotic treatment on the radiological and clinical outcome after ICH in a subgroup of patients included in a national registry. *Methods:* Based on the National Acute Stroke Israeli (NASIS) registry during 2004, 2007, 2010, and 2013 (2-month periods), characteristics, volumetric parameters, and prognosis of a subgroup of patients with ICH were analyzed. *Results:* Among the 634 patients with ICH in the NASIS registry, 310 (49%) were not treated previously with antithrombotic medications, 232 (37%) were treated with an antiplatelet agent, and 92 (14.5%) patients were on oral anticoagulant therapy, of them 30 patients (33%) with an international normalised ratio (INR) value below 2, 33 (36%) patients with an INR value of 2-3, and 29 patients (31%) with an INR value above 3 upon admission. Patients with deep hemorrhage on prior anticoagulants treatment had the highest probability for poor outcome at hospital discharge. Patients with low bleeding volume (0-30 cm^3), were likely to have admission National Institute of Health Stroke Scale < 10 (62%), while those with higher volumes (30-59 cm^3 and > 60 cm^3), had only 16.7% and 14.3% chance, respectively. We did not observe a significant difference between prior antithrombotic treatment and functional outcome at discharge, yet prior anticoagulant treatment was associated with higher long-term mortality rates. *Conclusions:* Our findings, based on a national registry, support the high mortality and poor outcome of anticoagulant related ICH.

Key Words: Intracerebral hemorrhage—antithrombotic—anticoagulation—outcome—prognosis

Introduction

Intracerebral hemorrhages (ICHs) constitute approximately 10%-20% of all strokes, and even higher in eastern Asia. However, they are the most devastating stroke subtype.[1-3] Only 12% of patients who had an ICH survived the event with only a minor deficit,[4] and mortality rates after an ICH account for a remarkably high proportion.[2] ICH incidence is about 4.3 per 10,000 person-years,[5] and mortality rates range from 30% to 55%.[4,6] Therefore, ICHs create a heavy socio-economic burden on society.[7]

The use of antithrombotic medications, such as antiplatelets and anticoagulants, is constantly increasing due to their ability to prevent thromboembolic events.[8] One percent of the European population, and in some countries even 1.7%, is regularly being treated with various types of

From the *The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; †The Israeli Association for Cardiovascular Trials, Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel; and §The Department of Neurosurgery, Rabin Medical Center, Petah Tikva, Israel.

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Address correspondence to Roy Romem, Sackler Faculty of Medicine, Tel Aviv University, P.O.B 39040, Tel Aviv 6997801, Israel. E-mail: royromem@mail.tau.ac.il

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oral anticoagulants (OAC).[9] Antithrombotic associated-ICH (AA-ICH) is one of the most formidable complications which could occur during an antithrombotic treatment.[10] Patients on long-term OAC treatment are at 7-10 times higher risk to develop AA-ICH than those who are not,[11] and about 25% of all ICH events are antithrombotic associated.[12,13] AA-ICHs were found to be more perilous, followed by worse functional outcome and higher mortality rates.[13-15] Due to its worse prognosis, and lack of sufficiently adequate treatment we aimed to analyze ICH and AA-ICH patients' baseline characteristics, radiographic evaluation, and outcome based on the National Acute Stroke Israeli (NASIS) registry. In addition, we assessed prognostic factors affecting these patients.

Methods

Study Design and Setting

The NASIS registry is conducted nationwide triennially, at all 28 hospitals admitting acute stroke in Israel. It is conducted by the Israeli Neurological Association in collaboration with the Israel Center for Disease Control, Israeli Ministry of Health and is under auspices of the Israeli Medical Association. A coordinating physician, nominated by each of the hospitals, is responsible for gathering the information for all admitted patient. Structured data forms are filled, including demographics, risk factors, clinical presentation, clinical diagnosis, treatment, complications, and outcome by the modified Rankin Scale (mRS). Stroke types (ischemic or ICH) are verified by head computed tomography (CT) or MRI, or otherwise regarded as undetermined (2%). For uniformity of data collection, study investigators receive a detailed study manual of operation and undergo specific training on details of data collection.

Patients with acute stroke (ischemic or ICH) or transient ischemic attack aged 18 and higher, admitted in any of the hospitals during 2-month periods (February to March 2004, March to April 2007, April to May 2010, and April to May 2013) were included in the NASIS registry. Admission policies of the registry had not been changed in Israel between the study periods. Patients with traumatic ICH and patients with epidural, subdural, or subarachnoid hemorrhage were not included in the registry. Mortality rates were provided and validated by means of matching patients' files with national mortality data.

Total number of registered patients was 8427, and 634 of them who had an ICH were included in our study. This ICH patients group was composed of those who had no prior antithrombotic treatment, and from those who had prior antiplatelet or anticoagulant therapies.

We further evaluated the radiographic features of a subgroup, including 188 patients who were hospitalized in 4 major, tertiary medical centers. CT scans were analyzed for ICH volume, perihematomal edema volume, sum of both volumes (regarded as total volume), for robust location (right or left hemisphere), infra or supratentorial location, as well as for lobar or deep (defined as basal ganglia, thalamus, brainstem, and cerebellum) hemorrhage.

Standard Protocol Approvals, Registrations, and Patient Consents

The NASIS registry was approved by the institutional ethical standards committees on human experimentation of all hospitals, permitting waivers of informed consent for this nationwide observational study.

Statistical Analysis

The groups were tested for univariate analysis with ANOVA and the chi-square test as appropriate for continuous and categorical variables, respectively. Whenever variables were not normally distributed, the Kruskal-Wallis test was performed. A multivariate logistic regression was carried out in order to assess the effects of explanatory variables on the outcomes: National Institute of Health Stroke Scale (NIHSS) $\geq$ 10 on admission and mRS at discharge $>$ 3. The results of the logistic regressions are presented as odds ratio (OR) (95% confidence interval [CI]) in a table and Forrest plot. OR (95% CI) $>$ 1 shows risk factors and OR (95% CI) $<$ 1 shows protective factors for fitted outcome. The impact of treatment type on 1-year survival is captured by Kaplan Meier curves and log-rank test for the difference in survival between the groups. Descriptive statistics was performed by boxplots for total volume. Multivariate analysis for the outcome *Total Volume* displayed in a linear regression, followed by a log-linear regression due to positive skewness in total volume distribution. Data analysis was carried out with R (R Foundation for Statistical Computing, Vienna, Austria). *P* values less than .05 were considered significant.

Results

A total of 634 patients who had an ICH during the 4 registry periods were investigated. The patients were divided into 3 groups according to the antithrombotic treatment they received prior to the hemorrhagic event; Group I—no prior antithrombotic treatment (310 patients, 49%); Group II—prior antiplatelet therapy (232 patients, 37%); and Group III—prior anticoagulant therapy (92 patients, 15%). Among patient in Group III, 30 (33%) were on a subtherapeutic INR value below 2, 33 patients (36%) were on INR range of 2-3, and 29 (31%) were on supratherapeutic values of above 3 upon hospital admission.

Comparison of the 3 groups regarding baseline characteristics, comorbidities, and NIHSS score on admission is presented in Table 1. Significant differences were noted amongst the 3 groups in age, hypertension, atrial fibrillation, congestive heart failure, prior coronory artery bypass graft/percutaneous coronary intervention, prior stroke,