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Full Length Article

Intracranial haemorrhage in patients treated with direct oral anticoagulants

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ABSTRACT

Introduction: Direct oral anticoagulants (DOAC) are increasingly used for the prevention and treatment of thromboembolic events. However, only little evidence is available regarding the management of patients who are treated with DOAC and present with potentially life-threatening intracranial haemorrhage. Herein, we describe our experience with respective patients treated at our institution.
Methods: We retrospectively analysed all consecutive patients with DOAC intake and intracranial haemorrhage treated at our institution from 09/2011 to 03/2015. Patient characteristics were analysed with specific focus on results of laboratory studies, treatment modalities and patient outcomes. Findings were compared between survivors (SV) and non-survivors (NSV) on day 30 after admission.
Results: A total of 55 patients were identified. The 30-day mortality rate in this patient cohort was 20.0%. Neurosurgical procedures were carried out in 37 patients (67%). Median values of international normalized ratio (INR) did not differ significantly between SV (1.11) and NSV (1.09). Renal function was significantly lower in NSV (median serum creatinine: 115 μmol/l) than in SV (median serum creatinine: 69 μmol/l; $p < 0.05$) and all patients with serum creatinine levels >125 μmol/l died during in-hospital treatment. Pro-haemostatic therapy with prothrombin complex concentrates (PCC) had no effect on INR in repeated measurements.
Conclusion: Our experience demonstrates that successful neurosurgical management of patients with intracranial haemorrhage and DOAC intake is feasible. However, drastic deterioration was observed in some patients, particularly when impaired renal function was present. The role of pro-haemostatic therapy with PCC is unclear. These findings underscore the urgent need of improving treatment modalities for these patients.

1. Introduction

The introduction of direct oral anticoagulants (DOAC: apixaban, dabigatran, rivaroxaban) has changed the current practice of anticoagulation therapy. Prospective controlled trials have demonstrated that DOAC are associated with similar or reduced rates of thromboembolic events compared with vitamin K antagonists (VKA). [1–4] Furthermore, major bleeding complications such as intracranial haemorrhage and fatal bleeding occur less frequently with DOAC than with VKA. Importantly, these findings seem to translate into a 'real world' setting outside clinical trials with first analyses of registry data confirming these favourable study results. [5,6] Despite these advantages, concerns regarding the lack of specific reversal agents for cases of haemorrhage currently exist. Guidelines for the management of bleeding complications are based on pathophysiological rationales and primarily rely on the results of pre-clinical studies. Several case reports have demonstrated the potential of DOAC to exacerbate intracranial haemorrhage with fatal patient outcomes. [7–9]

In this article we present the currently largest series regarding the management of patients treated with DOAC and suffering from intracranial haemorrhage. Patient characteristics including results of laboratory examination of haemostatic parameters and cerebral imaging studies were reviewed. Modalities of neurosurgical procedures and pro-haemostatic measures such as administration of prothrombin complex concentrates (PCC) were analysed. Furthermore, we report on the further in-hospital course and 30-day mortality rate of patients.

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2. Methods

This study was approved by the institutional review board. Data from all consecutive patients with a reported intake of apixaban, dabigatran, or rivaroxaban and treated for acute intracranial haemorrhage at the Department of Neurosurgery from September 2011 to March 2015 were included in this analysis (n = 55). We did not identify respective patients for the time period from April 2008 (introduction of DOAC) to August 2011. Patients were either referred from outside institutions (n = 31) or presented directly to our emergency department (n = 24). Baseline characteristics include age, gender, Glasgow Coma Scale (GCS) score, cerebral computed tomography (CCT) findings, comorbidities, concomitant medication intake and results of laboratory examination (INR, international normalized ratio; aPTT, activated partial thromboplastin time; PC, platelet count; serum creatinine). The Cockcroft-Gault formula was used to estimate the glomerular filtration rate (GFR). Calibrated chromogenic anti-Xa-assay results of rivaroxaban concentrations were available for 17 patients. The further clinical course was analysed regarding rate and kind of neurosurgical intervention, administration of pro-haemostatic substances, re-bleeding on CCT, laboratory findings, and 30-day mortality rate. The Outcome at hospital discharge was assessed according to the Glasgow Outcome Scale (GOS). Concomitant medication was analysed with specific focus on the presence of substances which have been previously identified to increase DOAC levels through drug interactions. [10]

All patients were treated according to standardized protocols for the treatment of (traumatic) intracranial haemorrhage. Blood samples for laboratory tests were obtained on hospital admission of patients. The decisions to administer pro-haemostatic substances and/or to perform emergency procedures were made by the neurosurgeon consultant on duty. Based on available guidelines [10], PCC was administered in the majority of patients. The dosage was at the discretion of the treating physician, but guideline recommendations (25 I.U.) were followed in the majority of cases. Two different PCC products were used depending on their availability: Beriplex P/N® (CSL Behring, Marburg, Germany) and Octaplex® (Octapharma, Langenfeld, Germany). In some cases, tranexamic acid (Cyklokapron®, Pfizer, Berlin, Germany) was also administered. In the patients' further courses, repeated CCT imaging was obtained if neurological deterioration occurred or concerns regarding the patient's re-bleeding risk were present.

For statistical comparison, the p values for categorical variables (gender, CCT findings, comorbidities, repeated CCT imaging, re-bleeding rate, death) were derived from the Fisher's exact test. For comparison of continuous variables (age, GCS scores, laboratory values) we used the two-sided student's t test. A p value of <0.05 was considered statistically significant. A univariate logistic regression was performed to ascertain the effect of described variables on the likelihood of 30-day mortality. Odds Ratio with corresponding .95 confidence intervals and two-sided p-values are reported. For the analysis of temporal evolvement of INR with regard to PCC administration, we analysed the temporal alteration and divided the time axis into three time frames (0 to 24 hours, 24 to 48 hours, and 48 to 72 hours following hospital admission). In the first method, we calculated the beta coefficient of a linear regression for each patient as a measure for the gradient and used it for group comparison. For the second method, we grouped patients into the described three time frames. If a patient had more than one measurement within a time frame, we calculated the median of replicated measurements for that time frame. Then, we made a group comparison for each time frame separately. The Mann–Whitney U Test was used for group comparison. All analyses were performed with GraphPad Prism 5 (GraphPad Software, La Jolla, USA) and R 3.1.3 with R package rms 4.2-1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 55 patients met inclusion criteria and characteristics are described in Table 1. The number of patients increased from 1 (2011) to 27 in 2014 (Fig. 1). Nine patients died during in-hospital treatment which resulted in an in-hospital mortality rate of 16.4%. The 30-day mortality rate was 20.0%. Importantly, 64% of deceased patients had admission GCS scores of 13–15. Repeated CCT was carried out in 40 patients (73%) and overall intracranial re-bleeding rate was 38%. The rates of repeated CCT, re-bleeding on CCT, and overall re-bleeding rate were significantly higher in NSV compared with SV ($p < 0.05$). The re-bleeding rate on CCT imaging in NSV was 91% and death was attributable to intracranial haemorrhage in 10 of 11 patients. Median values for INR and aPTT were not different between SV and NSV (Fig. 2A,B). No differences between anti-Xa levels were observed between both groups (Table 1). Median serum creatinine levels were significantly lower in SV (69 μmol/l) than in NSV (115 μmol/l) as well as median glomerular filtration rates (SV: 85 ml/min; NSV: 50 (ml/min); Fig. 2C,D). All patients with serum creatinine levels >125 μmol/l (n = 4) died during in-hospital treatment. There were no differences regarding the rate of concomitant antiplatelet therapy between both groups. No patient had concomitant medication which could have theroretically increased DOAC concentrations. Logistic regression analysis confirmed a strong association between serum creatinine, GFR and pre-existent renal insufficiency with 30-day mortality (Table 2). A trend toward significance was observed for male gender as a risk factor for 30-day mortality ($p = 0.0521$). Neurosurgical interventions were carried out in 37 patients (67%). PCC was administered in 31 patients (56%) and the median dosage was not different between SV and NSV (Fig. 3A). PCC administration was significantly associated with 30-day mortality. Repeated laboratory values (INR) were obtained in 42 patients and a total of 115 measurements were available for statistical analysis. No significant effects of PCC administration on results of repeated laboratory examinations of INR were observed (Fig. 3B-D). SV had a median GOS of 5 and 66% of survivors had a favourable outcome (GOS 4 and 5) at hospital discharge.

4. Discussion

The number of patients with an intake of DOAC and treated for intracranial haemorrhage at our institution continuously increased during the study period. This corresponds well with previous reports of rapid growth in the uptake of DOAC since their approval for patients with atrial fibrillation. [11] Intracerebral haemorrhage (ICH) is a well-recognized complication of antithrombotic treatment and may have devastating or even fatal consequences for affected patients. Several prospective randomized trials have demonstrated a significantly lower incidence of ICH in patients treated with DOAC than with VKA and first analyses of registries have confirmed these favourable findings. [6,12] In contrast to anticoagulation reversal protocols for the management of VKA-associated bleeding complications, no specific antidotes are currently available for DOAC reversal. This lack of antidotes has led to an intense debate regarding the safety profile of DOAC in patients with bleeding complications. [13] Several case reports and series have demonstrated the potential of DOAC to convert minor haemorrhage into fatal bleeding. Parra et al. have reported a mortality rate of 40% in dabigatran-treated patients who deteriorated after sustaining traumatic intracranial haemorrhage. [7] We have previously demonstrated that rivaroxaban intake may be associated with a higher risk of bleeding exacerbation compared with VKA or antiplatelet medication in patients with mild traumatic brain injury [14].

Results of studies focusing on the outcome of ICH patients have suggested that DOAC intake is not associated with increased mortality rates compared with VKA treatment [15,16]. Hartl et al. analysed data from 18'111 study participants of the RE-LY trial and found similar mortality rates for warfarin (36%) and dabigatran (38%) in 154 patients