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Coagulation Testing in Intracerebral Hemorrhage Related to Non-vitamin K Antagonist Oral Anticoagulants

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Abstract

Background Intracerebral hemorrhage (ICH) is a life-threatening complication of non-vitamin K antagonist oral anticoagulants (NOAC). Little is known about the effect of intensity of anticoagulation on NOAC-ICH. We describe the current use of coagulation testing in the emergency setting and explore associations with baseline size and expansion of hematoma as determined in a previous study.

Methods Data from the prospective multicenter RASUNOA registry were analyzed. Patients with NOAC-ICH were enrolled between February 2012 and December 2014. Frequency of local test performance of specific (anti-factor Xa tests, diluted thrombin time) and non-specific tests (international normalized ratio (INR), activated partial thromboplastin time (aPTT), thrombin time) was analyzed. The association of anticoagulation intensity at admission with hematoma volume and hematoma expansion was explored.

Results In 61 NOAC-ICH patients enrolled at 21 centers, drug-specific coagulation testing was performed in 16 cases (26%), and only 29% of centers appeared to use drug-specific tests in NOAC-ICH at all. In some cases, INR and aPTT values were normal despite drug concentrations in the peak range. In patients with available drug-specific concentrations, 50% had drug levels in the peak range at admission. Higher intensity of anticoagulation was not associated with higher hematoma volume at admission or with subsequent hematoma expansion.

Conclusion Drug-specific tests are only infrequently used in NOAC-ICH. Normal results in non-specific coagulation do not reliably rule out peak range concentrations. Anticoagulation intensity at admission does not predict baseline hematoma volume or subsequent hematoma expansion.

Keywords Stroke · Intracerebral hemorrhage · Anticoagulation · Laboratory testing · Oral anticoagulants

Introduction

Intracerebral hemorrhage (ICH) is the most feared complication of long-term anticoagulation. Recent findings suggest that ICH related to non-vitamin K antagonist oral anticoagulants (NOAC) has similar features regarding hematoma expansion and carries the same dismal prognosis as ICH related to vitamin K antagonists (VKA) [1]. Similar to VKA-ICH, emergency reversal of anticoagulation is recommended in NOAC-ICH to prevent hematoma expansion [2]. While coagulation status in VKA-ICH can be rapidly assessed by measuring the international normalized ratio (INR), with point-of-care tests allowing

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bedside INR measurements even before administration of reversal therapy [3], coagulation testing in NOAC-ICH is more complex and time-consuming and differs among agents. In contrast to specific tests including calibrated anti-Xa levels for factor Xa inhibitors and the Hemoclot assay for dabigatran, routine non-specific coagulation tests such as the activated partial thromboplastin time (aPTT) and the INR have limited capability for reliable detection of the anticoagulant effect of NOACs [4]. The current practice of coagulation testing in routine ICH care is unknown. Furthermore, it is unclear whether the intensity of anticoagulation with NOAC measured at admission correlates with hematoma size at presentation and with subsequent hematoma expansion.

Herein we report the current use of non-specific and specific coagulation testing in ICH patients on treatment with NOAC who were enrolled into the multicenter, prospective registry of acute stroke under new oral anticoagulants (RASUNOA). We also explore potential associations between the intensity of anticoagulation and baseline hematoma volume and hematoma expansion.

Methods

Study Design, Setting, and Patients

Adult patients with non-traumatic ICH and current use of a NOAC (i.e., apixaban, dabigatran or rivaroxaban) were prospectively enrolled between February 2012 and December 2014 into the RASUNOA registry at 21 actively participating centers across Germany (ClinicalTrials.gov, NCT01850797). Approval was obtained from the ethics committee of the Medical Faculty of Heidelberg, Germany, as well as from the ethics committees of each participating center.

RASUNOA was an observational study. Accordingly, all diagnostic and treatment decisions were left at the discretion of the local treating physicians and any local standard-operating procedures regarding the use of specific or non-specific coagulation tests were not influenced.

Results of non-specific coagulation tests (aPTT, ecarin clotting time, thrombin time [TT], or INR) and drug-specific coagulation tests (anti-factor Xa or Hemoclot assay [diluted thrombin time]) as well as renal function (creatinine and glomerular filtration rate) were obtained at admission and reported using pre-specified case report forms (CRF) (see online supplemental for reference ranges of laboratory parameters). Medical history, symptom onset, clinical course, and the time of last NOAC intake were documented using the CRF.

Details of the hematoma analysis are described in the previously published main analysis of the RASUNOA ICH substudy [1]. We performed central imaging analysis. Hematoma volume was assessed using a semiplanimetric approach by 2 independent, experienced readers, which were masked to all patient characteristics. Arithmetic means of the volumes determined by the 2 readers using the region-of-interest volume calculator in OsiriX (Pixmeo, Switzerland) were used for further analysis. Consensus between the two readers was sought in case of volume differences ($>30\%$) or technical problems. Substantial hematoma expansion was pre-specified as an increase in hematoma volume of $\geq 33\%$ or ≥ 6 ml absolute.

Statistics

Mean and standard deviation (SD) were used for description of continuous variables. For categorical variables, median and interquartile range (IQR), and absolute and relative frequencies were reported. For correlation between non-specific and specific coagulation test values and baseline hematoma volume, the Spearman's nonparametric correlation was applied. Analysis of differences in the hematoma expansion group was limited to patients with follow-up-imaging. Additionally, linear regression analysis for log-transformed baseline hematoma volume (to approximate normal distribution) was performed. All statistical tests were two-sided, and p values of <0.05 were considered statistically significant. If not indicated otherwise, analyses were conducted using IBM SPSS Statistics, version 23.0.0.2 (IBM SPSS, Armonk, NY, USA).

Results

Sixty-one patients (mean age 76 years, 41% women, Table 1) with ICH related to NOAC were prospectively enrolled into RASUNOA. Patients presented within a median of 10.7 h (IQR 4.4–26.5) after last NOAC intake (Table 1). The radiological and clinical courses have been previously described in detail [1]. Briefly, the median baseline hematoma volume was 11 ml (IQR 4–30). Follow-up imaging was available in 45/61 patients, of whom 38% (17/45) had substantial hematoma expansion [1]. As previously reported, patients with concomitant platelet-inhibitor treatment (6/61) were older and suffered from larger baseline hematoma volumes [1]. However, concomitant platelet-inhibitor treatment was not associated with a higher number of substantial hematoma expansions in this small subgroup.

Non-specific Coagulation Testing

Non-specific coagulation tests were available in 97% of patients (Table 2). Results of non-specific tests are

Table 1 Patient characteristics

	Patients ($n = 61$)
Age, years; mean (SD)	76.1 (11.6)
Women; *n* (%)	25 (41)
NOAC; *n* (%)	
Apixaban	5 (8)
Dabigatran	7 (12)
Rivaroxaban	49 (80)
Indication for oral anticoagulation; *n* (%)	
Atrial fibrillation	59 (97)
Venous thromboembolism	2 (3)
Concomitant antiplatelet therapy; *n* (%)[a]	6 (10)
Renal function at admission	
GFR, ml/min; median (IQR),	66.4 (59.0–81.5)
GFR $<$ 60 ml/min; *n* (%)	16 (29)
Time since last intake NOAC until admission, hours; median (IQR)[b]	10.7 (4.4–26.5)
Time from last intake NOAC to symptom onset; median (IQR)[c]	10.0 (0.5–30.0)

GFR electronic glomerular filtration rate, *NOAC* non-vitamin K antagonist oral anticoagulant

[a] Apixaban: none, dabigatran: 1 patient clopidogrel, rivaroxaban: 5 patients aspirin and/or clopidogrel

[b] Data available for $n = 38$, and $n = 36$ patients, resp

[c] In two cases, it cannot be fully excluded from medical history that there was further intake shortly after first symptoms started. In both cases, small baseline hematoma volumes and no hematoma expansion were observed (table adapted from [1])

Table 2 Availability of key coagulation laboratory parameters in clinical routine by NOAC

	All	Dabigatran	Rivaroxaban	Apixaban
N (Patients)	61	7	49	5
INR; *n* (%)	59 (97)	6 (86)	49 (100)	4 (80)
aPTT; *n* (%)	56 (92)	6 (86)	48 (98)	2 (40)
TT; *n* (%)	27 (44)	5 (71)	21 (43)	1 (20)
Anti-Xa (drug-specific); *n* (%)	–	–	18 (37)	2 (40)
Calibrated; *n* (%)	–	–	13 (27)	0 (0)
ECT; *n* (%)	–	2 (29)	–	–
Dabigatran concentration; *n* (%)	–	3 (43)	–	–

aPTT activated partial thromboplastin time, *ECT* ecarin clotting time, *INR* international normalized ratio, *NOAC* non-vitamin K antagonist oral anticoagulant, *TT* thrombin time

summarized in Supplementary Table ST2. Both aPTT and INR were correlated with simultaneously determined rivaroxaban concentration (aPTT, Spearman $r = 0.63$, 95% CI 0.11–0.88, $p = 0.024$; INR, $r = 0.81$, 95% CI 0.46–0.94, $p = 0.001$; $n = 13$). However, as illustrated in Fig. 1b, some patients on rivaroxaban had normal aPTT and INR values despite drug concentrations in the peak range. The aPTT, INR and TT were elevated in the presence of dabigatran concentrations >100 ng/ml, but the number of paired samples was too small for further statistical analysis, and cases with lower dabigatran concentrations <100 ng/ml were not available ($n = 3$; Fig. 1a).

Specific Coagulation Testing

Only a minority of centers appeared to perform drug-specific tests in patients with acute NOAC-ICH (6/21; 29%). In these centers, drug-specific coagulation tests were performed in 26% (16/61) of the NOAC-ICH patients. At admission, tests indicated peak range concentrations in 50% (8/16). Patients who were treated subsequently with prothrombin complex concentrate (PCC) were more frequently tested with drug-specific tests than patients who did not receive a reversal treatment for anticoagulation (Supplementary Table ST3). However, drug-specific

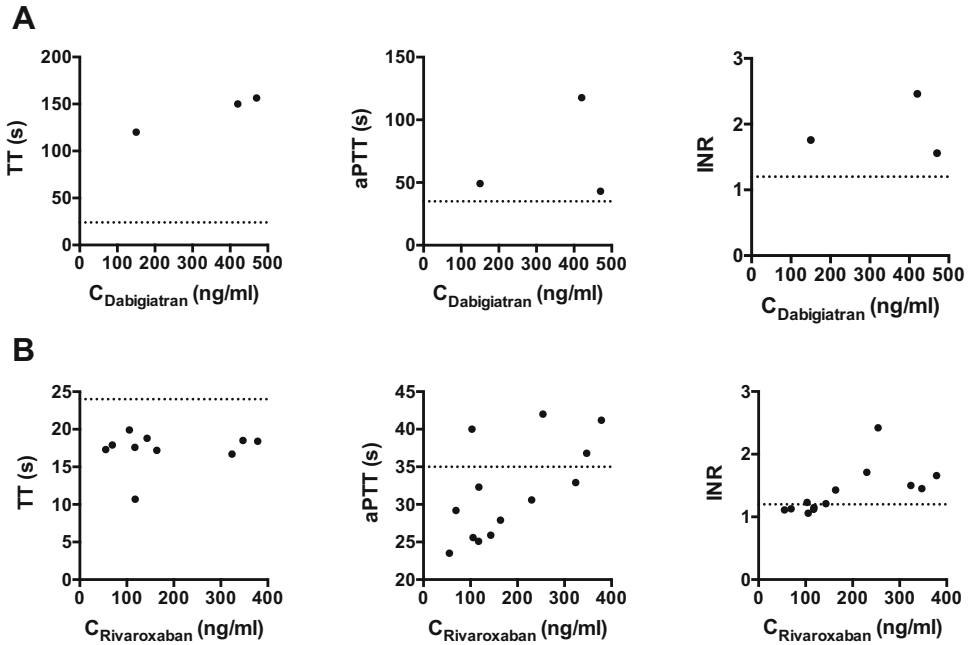

Fig. 1 **a**, **b** Correlation of routine coagulation tests with NOAC concentrations at admission (**a** dabigatran, **b** rivaroxaban). *Dotted lines* represent the upper range of normal. Due to the limited sample number for apixaban, plots are exclusively shown for dabigatran and rivaroxaban

concentrations at baseline did not statistically differ between PCC-treated patients vs not-treated ($p = 0.78$).

Admission Coagulation Status and Hematoma Volume

In univariate logistic regression analysis, there were no significant differences of non-specific coagulation test results obtained at admission and baseline hematoma volume, except for a smaller hematoma volume in patients with higher aPTT (Table 3). We also did not find any significant difference between hematoma volumes in patients with elevated coagulation test parameters and parameters within normal range (Supplementary Table ST4). Furthermore, time since last NOAC intake to onset was not associated with baseline hematoma volume (data not shown). There was also no significant association between coagulation intensity at admission and substantial hematoma expansion (Table 4).

Discussion

The two main findings of our study are that (1) in most patients with NOAC-ICH the coagulation status is currently only tested using non-specific tests and (2) anticoagulation intensity as measured by anticoagulant-specific tests is associated neither with baseline hematoma volume nor with subsequent hematoma expansion.

Our study further highlights that non-specific global routine tests cannot reliably distinguish between low and high drug concentrations in NOAC-ICH. This is consistent with findings in acute ischemic stroke patients on treatment with NOACs [4]. Results of non-specific coagulation tests in the context of stroke on NOACs must therefore be interpreted with great caution. Especially in case of the frequently prescribed factor Xa inhibitors, physicians must be aware of the different sensitivities of reagents used to determine the INR, with some reagents being highly sensitive (e.g., Neoplastin Plus), whereas others are almost

Table 3 Association between coagulation tests and hematoma volume at baseline (univariate linear regression)

	All			Rivaroxaban		
	β	95%-CI	*p*	*β*	95%-CI	*p*
INR	−0.975	−2.08–0.131	0.083	−0.728	−1.965–0.510	0.24
aPTT (s)	−0.030	−0.056 to −0.004	0.024	−0.033	−0.073–0.006	0.095
TT (s)	−0.002	−0.014–0.011	0.76	−0.001	−0.026–0.024	0.95
Calibrated anti-Xa test[a]				−0.004	−0.010–0.002	0.17

Hematoma volume at baseline = log-transformed. *aPTT* activated partial thromboplastin time, *INR* international normalized ratio, *TT* thrombin time

Due to the sample number, individual data are exclusively shown for rivaroxaban

[a] p values of <0.05 (two-sided tests) were considered statistically significant

Table 4 Admission coagulation status and hematoma expansion per NOAC

	Rivaroxaban			Apixaban		
	HE ($n = 14$)	No HE ($n = 23$)	p	HE ($n = 2$)	No HE ($n = 1$)	p
INR; median (IQR)	1.2 (1.1–1.3)	1.3 (1.1–1.5)	0.23	1.2 (1.2–1.2)	1.1 (–)	0.67
aPTT, s; median (IQR)	31 (26–37)	32 (29–40)	0.39	nd	30 (–)	nd
TT, s; median (IQR)	18 (17–19)	17 (15–19)	0.26	nd	16.8 (–)	nd
Calibrated anti-Xa test[a], ng/ml; median (IQR)	150 (59–341)	254 (110–335)	0.56	–		

Patients receiving dabigatran ($n = 7$) were excluded from this analysis because no substantial hematoma expansion was observed. *aPTT* activated partial thromboplastin time, *HE* hematoma expansion, *INR* international normalized ratio, *TT* thrombin time

[a] p values of <0.05 (two-sided tests) were considered statistically significant

insensitive (e.g., Innovin) [5]. With apixaban, a low sensitivity with all current used reagents is observed [6]. The relevance of this finding for NOAC-ICH patients is that normal non-specific coagulation test results should not be misinterpreted as showing no effective anticoagulation which may influence the decision to reverse or not to reverse anticoagulation.

Despite the shortcomings of non-specific tests, the more sensitive drug-specific tests were only performed in 26% of the NOAC-ICH patients in our study and only by a minority of stroke centers although most sites participating in our study were major stroke centers.

Current thinking is that ICH related to oral anticoagulation is not the result of anticoagulation itself but that anticoagulation exacerbates a spontaneously occurring bleeding [7]. Nevertheless, in patients using VKA, the risk of ICH exponentially increases with the intensity of anticoagulation as measured by the INR but 2/3 of VKA-related ICH occurs albeit INR values within the target therapeutic range (i.e. INR 2–3) [8]. In patients treated with dabigatran, the risk of all major bleedings increases with rising dabigatran steady-state trough concentrations [9]. Similarly, patients receiving edoxaban have a higher bleeding risk with higher trough levels compared to a dosing regime with higher peak levels [10]. Taken together, these data suggest an association of anticoagulant intensity (particularly trough) with the incidence of major bleedings.

It is less clear whether there is also an association between anticoagulant activity at the time of the ICH and hematoma size. We did not find an association between NOAC level—as determined by drug-specific tests—and hematoma size at baseline. The observed association between higher aPTT levels and smaller hematoma volumes is most likely a small-number effect, but requires replication in a larger cohort. Similarly, a baseline INR below 3.0 is not associated with the baseline hematoma volume in VKA-related ICH [11]. Attributing hematoma size to intensity of anticoagulation by VKA and NOAC alone might thus be oversimplified, and other factors such as blood pressure should be considered in future studies.

Our data also suggest that the NOAC anticoagulant intensity at admission is not a predictor for subsequent hematoma expansion. The relevance of this observation for NOAC-specific emergency coagulation testing in NOAC-ICH patients on admission and for reversal treatment requires further investigation. In VKA-related ICH, the baseline INR is also not associated with hematoma expansion but rapid effective INR reversal (INR $\leq$ 1.3) can prevent hematoma expansion [12]. Thus, in VKA-ICH, reversal treatment with PCC is recommended based on findings from clinical trials of VKA reversal in systemic and intracranial bleeding [13, 14]. Although immediate reversal attempts are currently also recommended for NOAC-ICH in analogy to VKA-related ICH, the usefulness of coagulation testing at the time of diagnosis and for monitoring the effectiveness of anticoagulant reversal treatment remains to be defined. While anticoagulant reversal of dabigatran with idarucizumab is usually definitive [15], reversal with andexanet alfa may require laboratory monitoring and dosing adjustments [16].

The main limitations of our study are the small sample size and the limited availability of specific coagulation test results. However, this is the only study examining laboratory testing in NOAC-ICH to date. Moreover, we had to rely on information provided by patients and caregivers regarding the time of last NOAC intake rather than on a documented exact time point.

Conclusion

Drug-specific tests are not widely used in NOAC-ICH at present although non-specific global coagulation tests cannot reliably rule out relevant anticoagulant activity of NOACs. As we found no association of anticoagulant

intensity at admission with either baseline hematoma volume or subsequent hematoma expansion, the role of (specific) anticoagulant testing in NOAC-ICH remains to be defined in larger studies.

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Compliance with Ethical Standards

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