Coagulation Profile after Spontaneous Intracerebral Hemorrhage: A Cohort Study

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Background: Intracerebral hemorrhage (ICH) causes death or disability and the incidence increases with age. Knowledge of acute hemostatic function in patients with ICH without anticoagulant and antiplatelet therapy is sparse. Increased knowledge of the coagulation profile in the acute phase of ICH could improve acute treatment and recovery. We investigated coagulation at admission and changes in coagulation during the first 24 hours after symptom onset. *Methods:* Enrolled were 41 ICH patients without anticoagulant or antiplatelet therapy admitted to Aarhus University Hospital, Denmark. Blood samples were collected at admission, 6, and 24 hours after symptom onset. Thromboelastometry (ROTEM), thrombin generation, and thrombin-antithrombin (TAT) complex were analyzed. Clinical outcome was evaluated using the National Institute of Health Stroke Scale, the Modified Rankin Score, and mortality. *Results:* At admission, compared with healthy individuals, ICH patients had increased maximum clot firmness (EXTEM $P < .0001$; INTEM $P < .0001$; FIBTEM $P < .0001$), increased platelet maximum clot elasticity ($P < .0001$) in ROTEM, higher peak thrombin ($P < .0001$) and endogenous thrombin potential ($P = .01$) in thrombin generation, and elevated TAT complex levels. During 24 hours after significantly, while thrombin generation showed decreased peak thrombin ($P < .0001$) and endogenous thrombin potential ($P < .0001$). Coagulation test results did not differ between patients when stratified according to clinical outcome. *Conclusions:* ICH patients without anticoagulant or antiplatelet therapy demonstrated activated coagulation at admission and within 24 hours after symptom onset.

Keywords: Cerebral hemorrhage—thromboelastography—hemostasis—blood coagulation tests—S100B protein

Introduction

Intracerebral hemorrhage (ICH) causes death or disability with an annual incidence of 10-30 per 100,000,[1,2] and incidence is expected to increase due to increasing median life expectancy in the general population.[3] The treatment strategy of interest is to prevent further cerebral hemorrhage and thereby improve outcome. Currently, no

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specific hemostatic agent is able to stem the hemorrhage.[4] Therefore, increased knowledge of the effects of ICH on systemic coagulation, and especially information on coagulation in the acute phase, is needed.

Previous studies of patients with ICH have focused primarily on measurements of conventional coagulation assays like activated partial thromboplastin time (aPTT), prothrombin time, fibrin d-dimer, fibrinogen degradation products, and thrombin-antithrombin (TAT) complex. Overall, these assays indicate activated coagulation within the first 24 hours of ICH,[5-13] including elevated TAT complex levels [6,7,12] and elevated fibrin d-dimer, [7,9,10,12,14] the latter being correlated with poor outcome.[12,13,15]

Some studies enrolled patients who had been prescribed anticoagulant or antiplatelet therapy [5,12] or there was no information included concerning this issue.[6,9,10,16] However, this information is crucial as anticoagulant and antiplatelet therapy influences outcome after ICH.[17-20]

Thromboelastometry (ROTEM) provides a dynamic whole blood coagulation profile.[21,22] Recent years have seen increasing use of ROTEM in bleeding patients as this diagnostic strategy has contributed to a reduction in proportion of transfused patients.[23] Thrombin generation assesses the dynamically generated amount of thrombin but is so far mainly used as a research tool.[24] The TAT complex consists of inactive thrombin and anti-thrombin, and TAT complex levels reflect the extent of endogenous thrombin generation.[25]

The aim of the present study was to explore the possible changes induced by ICH in patients without anticoagulant or antiplatelet therapy immediately after admission to hospital, and 6 and 24 hours after symptom onset employing a wide range of dynamic coagulation assays. We hypothesized that ICH patients displayed systemically activated coagulation in the acute phase compared with healthy individuals.

Materials and Methods

Study Population

This prospective cohort study included 41 patients with ICH from 18 June 2014 to 31 August 2016. Patients were enrolled at the Department of Neurosurgery and the Department of Neurology, Aarhus University Hospital, Denmark. Blood samples were collected at admission (admission sample), at 6 hours (±2 hours) (sample 2), and 24 hours (±2 hours) (sample 3) after symptom onset. Part of this study population has been presented previously.[26]

Inclusion criteria were: (1) hemorrhage diagnosed by cerebral computed tomography (CT) or magnetic resonance imaging (MRI); and (2) symptom onset of ICH within 6 hours before enrolment. Exclusion criteria were treatment with antithrombotic or antiplatelet drugs, age below 18 years, ischemic stroke within the previous 3 months, pregnancy, bleeding disorder, active cancer or chemotherapy within the past 3 months, liver cirrhosis, current infection, and hemorrhage triggered by arteriovenous malformation, brain tumor, or trauma.

Clinical data were obtained from medical records. We documented the Glasgow Coma Scale at admission. The National Institutes of Health Stroke Scale (NIHSS) was documented at admission[33;] and if patients were in a coma; NIHSS was estimated to be 38.[27] The Acute Physiology and Chronic Health Evaluation Score was calculated during the first 24 hours of hospitalization. Clinical outcome was evaluated after 30 days using the Modified Rankin Scale (MRS), and 30-days mortality was registered. ICH volume was calculated using the ABC/2 method, based on the obtained MRI or CT admission scan.[28] A follow-up scan was performed only on the demand of the attending physician. Significant hematoma expansion was defined as a proportional increase exceeding 33% or an absolute increase exceeding 6 mL from the initial ICH volume.[14,29]

The Regional Ethics Committee of Central Denmark approved the study (incompetent patients case no. 1-10-72-95-14, version 3, 05052014 and competent patients case no. 1-10-72-94-14, version 4, 27042014). All patients or their legal proxies provided written informed consent before study enrolment. The Danish Data Protection Agency also approved the study (incompetent patients case no. 1-16-02-225-14 and competent patients case no. 1-16-02-224-14). The Helsinki Declaration was followed in all aspects.

Laboratory Analyses

Blood samples were drawn from an antecubital vein or via an arterial cannula. The first tube was discarded. Whole blood for ROTEM (Tem International GmbH, Munich, Germany) was sampled in 3.5 mL tubes containing 3.2% sodium citrate (Vacuette® Greiner Bio-One GmbH, Kremsmünster, Austria). Analyses were performed within 2 hours from blood sampling using three standard assays: EXTEM (extrinsically activated), INTEM (intrinsically activated), and FIBTEM (fibrinogen specific). The ROTEM analyses were performed by the researchers. The following ROTEM parameters were obtained: clotting time, clot formation time, maximum velocity of clot formation (MaxVel), time to maximum velocity (t, MaxVel), and maximum clot firmness (MCF). Calculation of the platelet component, maximum clot elasticity (platelet MCE), was derived from the results of ROTEM tests performed with and without platelet inhibition according to Solomon et al.[30] First, MCE was calculated for both EXTEM MCF and FIBTEM MCF using the formula: $MCE = (100 \times MCF)/(100-MCF)$ for each assay. Second, clot elasticity attributable to platelets was calculated: MCE platelets = MCE EXTEM − MCE FIBTEM.[30]

ROTEM reference intervals and data for healthy individuals have been established by the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark,