Activation of blood coagulation after aneurysmal subarachnoid haemorrhage: a prospective observational trial by rotational thromboelastometry (ROTEM®)

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ROTEM® for coagulation monitoring after aSAH

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ABBREVIATIONS AND ACRONYMS

aSAH Aneurysmal subarachnoid haemorrhage
CFT clot formation time
CT clotting time
DCI delayed cerebral ischemia
DVT deep venous thrombosis
EBI early brain injury
EXTEM tissue factor activated, citrated and recalcified analysis
FIBTEM tissue factor plus platelet inhibitor cytochalasin D activated, citrated and recalcified analysis
GOSe extended Glasgow Outcome Score
ICU intensive care unit
INTEM contact activated, citrated and recalcified analysis
IQR interquartile range
MCF maximal clot firmness
PE pulmonary embolism
ROTEM® Rotational thromboelastometry
TEG® thromboelastography
VTE venous thromboembolism
SUMMARY

Objectives: Aneurysmal subarachnoid haemorrhage (aSAH) is reported to actuate blood coagulation. Rotational thromboelastometry (ROTEM®) is a dynamic haemostatic test that can differentiate various coagulation abnormalities, for example, increased coagulation activity can be detected as a wider amplitude of tracing (maximal clot firmness [MCF]). Previously, ROTEM® has not been used to evaluate coagulation changes after aSAH. The aim of this prospective, observational study was to evaluate the on-going coagulation process in patients with aSAH by comparing their ROTEM assay results to the control values obtained from patients undergoing clipping of non-ruptured aneurysms. Methods: ROTEM® analyses were performed at 12, 24, 48, and 72 hours after onset of aSAH and were compared with preoperative analyses of the control group. In total, 17 aSAH treated in the intensive care unit and 16 control patients were enrolled. Results: At 72 hours, EXTEM-MCF was significantly higher in aSAH patients compared with the baseline value of the control group (68.0 mm [interquartile range, IQR] 66.0–71.0 mm] vs. 64.5 mm [IQR, 59.5–66.8 mm]; $P = 0.024$). This was mainly due to increased fibrin formation and fibrin polymerisation as the same comparison in FIBTEM-MCF analysis yielded similar results (23.0 mm [IQR, 19.0–25.0 mm] vs. 15.4 mm [IQR, 12.5–17.8 mm], respectively; $P=0.001$). Conclusions: Blood coagulation is activated at 72 hours after onset of aSAH, which can be detected by ROTEM® EXTEM-MCF analysis. At the same time, FIBTEM-MCF was elevated, implying that relative contribution of fibrin formation and fibrin polymerisation are essential.
INTRODUCTION

The annual incidence of aneurysmal subarachnoid haemorrhage (aSAH) is falling, but its one-year mortality remains nearly at 50%. Among aSAH survivors, both early brain injury (EBI) and delayed cerebral ischemia (DCI) are major risk factors for poor neurological outcome and increased mortality. EBI is defined as early neurological deterioration caused by transient direct toxic effects from an initial haemorrhage, whereas DCI is delayed brain injury presenting as either as clinical deterioration or cerebral infarction. Still, the pathophysiology of these two entities is not fully understood.

Blood coagulation and fibrinolytic systems seems to activate during the acute phase of aSAH and increased coagulation can be detected from minutes following initial haemorrhage. However, association of cerebral microthrombosis with EBI or DCI has not been unequivocally determined in the clinical setting.

Viscoelastic point-of-care coagulation tests (e.g., rotational thromboelastometry [ROTEM®]) are thought to be advantageous compared with conventional laboratory tests when analysing the increased coagulation. No studies have investigated the on-going coagulation process after aSAH using ROTEM®. Our main aim was to assess ROTEM® measurements after aSAH and analyse the role of platelets and fibrinogen on clot formation. We also examined association of ROTEM® assay results with clinical events such as EBI and DCI.
MATERIAL AND METHODS

This prospective, observational clinical study was conducted in the intensive care unit (ICU) and neurosurgical department of Tampere University Hospital, Finland, between October 2015 and June 2016. The trial was conducted in accordance with the amended Declaration of Helsinki. The study design was approved by the local ethics committee of Pirkanmaa (230215-1) and was registered in the Clinical Trials database (ClinicalTrials.gov: NCT02540005). Written informed consent was obtained from all patients or their next of kin prior to study enrolment.

Study subjects

Consecutive patients with acute aSAH who were admitted to the ICU within 12 hours from the onset of aSAH symptoms (defined as sudden severe headache or loss of consciousness), and expected to stay in the ICU for at least 72 hours, were considered eligible. Subarachnoid bleeding was diagnosed with non-contrast computed tomography of the brain. A ruptured aneurysm as a source of haemorrhage was confirmed by either computed tomography angiography or digital subtraction angiography. Exclusion criteria were: age < 18 years, pregnancy, anticoagulant medication in regular use, and known active cancer. Only acetylsalicylic acid (< 150 mg daily) was allowed as an antithrombotic medication. Patients undergoing elective non-ruptured intracranial aneurysm clipping were chosen as the control group because they present the same disease entity and thus offering the closest surrogate values for pre-bleeding state prior aSAH. The control group served also as a local reference group for ROTEM®.
Clinical management

All aSAH patients received neurointensive care based on international guidelines.\textsuperscript{14,15} This included thromboprophylaxis therapy (tinzaparin 4500 IU subcutaneously, once daily) after occlusion of the ruptured aneurysm by either endovascular coiling or surgical clipping\textsuperscript{16}. After tinzaparin was started, no mechanical thromboprophylaxis was used.\textsuperscript{17} All control patients were treated according to perioperative protocols.

In addition to our standard neurointensive care, a bilateral compression ultrasound of the lower extremity veins to exclude asymptomatic deep venous thrombosis (DVT) was performed by radiologist once over days 3 to 5. When necessary, a computed tomography pulmonary angiogram was performed to rule out pulmonary embolism (PE).

Blood sampling

Blood samples for ROTEM\textsuperscript{®} analysis were retrieved from aSAH patients at 12, 24, 48, and 72 hours after onset of aSAH symptoms and compared to the preoperative samples of the control group (i.e., baseline). Complete blood, platelet, and leukocyte counts, serum C-reactive protein, and International Normalised Ratio concentrations were measured daily during the study period.
All blood samples from the aSAH and the control group were taken from a heparin-naïve arterial line.

**Thromboelastometry**

All ROTEM® assays were performed in the central laboratory of Tampere University Hospital using a ROTEM® delta analysis system (TEM Innovations GmbH, München, Germany). The following parameters were measured: clotting time (CT) (which represents time to initiation of clot formation), clot formation time (CFT) (which represents stabilisation of the clot), and maximum clot firmness (MCF) (which represents maximum clot strength). Each analysis was performed using single-use reagents. EXTEM measures coagulation activated by the extrinsic pathway, FIBTEM formation of fibrin-based clots after platelet inhibition by cytochalasin D to block the function of GPIIb/IIIa receptor and INTEM clot formation via contact phase. In general, a hypercoagulable state can be detected if MCF is elevated. Using different reagents, the impact of platelets and fibrinogen (EXTEM-MCF) and fibrin formation and its polymerisation (FIBTEM-MCF) on clots can be distinguished.

Our primary outcome was the EXTEM-MCF value in the aSAH patient group compared with the baseline value from the control group. Secondary outcomes were: other ROTEM® parameters (i.e., EXTEM-CT, EXTEM-CFT, FIBTEM-MCF, INTEM-MCF, INTEM-CT, and INTEM-CFT) compared with baseline values from the control group. To identify the platelet
contribution to cloth strength, the difference between EXTEM-MCF and FIBTEM-MCF was calculated.

Clinical and outcome measures

Clinical severity of aSAH at admission was reviewed retrospectively using the Hunt–Hess grade, from which EBI severity was classified as severe (Hunt–Hess, 4–5) or mild (Hunt–Hess, 1–3).\textsuperscript{19} Severity of bleeding was evaluated from the primary head computed tomography using the Fisher scale,\textsuperscript{20} and defined as moderate to severe if the scale was ≥ 3. Moreover, DCI was evaluated retrospectively from the intensive care database (Centricity Critical Care Clinisoft®; GE Healthcare, Barrington, IL, USA) at 24 hours to 14 days from the onset of aSAH symptoms using criteria presented by Vergouwen \textit{et al.}\textsuperscript{8} Briefly, DCI was defined as neurological deterioration (reduction in Glasgow Coma Scale by two or more points) for at least one hour, a new neurological symptom for at least one hour that cannot be explained by other features or a new ischemic episode on neuroimaging data that was not related to primary aSAH or neurosurgery.

Clinically significant events representing the hypercoagulable state were evaluated e.g., VTE including DVT and PE. Extended Glasgow Outcome Score (GOSe)\textsuperscript{21} (including mortality) was registered on day 90.

Statistical analysis
Statistical analyses were performed using the SPSS statistical software program (version 23.0, released 2015; IBM, Armonk, NY, USA). Depending on the distribution of variables, comparisons between continuous variables were performed using either the Mann-Whitney $U$-test or Student’s $t$-test. For categorical variables, univariate analysis with Fisher’s exact test was performed.

Based on the standard sample size calculations, at least 16 patients in each group was needed to detect a clinically significant increase in MCF (mm), from 65 mm to 70 mm, SD 5 mm by EXTEM S reagent, assuming a power of 80% and a significance level of 5%.

RESULTS

In total, 17 aSAH and 16 control patients were enrolled. The groups did not differ in sex, comorbidities, or body mass index, but the proportion of smokers was higher and patients were younger in the aSAH group (Table 1). Moreover, the ruptured aneurysm was more commonly located in the anterior communicating artery in the aSAH group, whereas most aneurysms in the control group were located in the middle cerebral artery (Table 1). In the majority of aSAH patients, bleeding was classified as moderate to severe and the aneurysm was repaired by endovascular coiling in 76.5% of patients ($n = 13$) (Table 2). On day 90, nearly 60% of aSAH patients showed good neurological recovery and mortality was 5.9%. More detailed demographic information on the aSAH patient group is shown in Table 2.
At 72 hours, EXTEM-MCF was significantly higher in aSAH patients compared with the baseline value from the control group: (68.0 mm [interquartile range {IQR}, 66.0–71.0 mm] vs. 64.5 mm [IQR, 59.5–66.8 mm], respectively; \( P = 0.024 \)). FIBTEM-MCF was also significantly increased at 72 hours compared with the baseline value from the control group: (23.0 mm [IQR, 19.0–25.0 mm] vs. 15.4 mm [IQR, 12.5–17.8 mm], respectively; \( P = 0.001 \)). The difference between EXTEM-MCF and FIBTEM-MCF represents platelet contribution to clot formation. This decreased significantly during the first 72 hours (48.5 mm [IQR, 46.3–50.8 mm] to 44.0 mm [IQR, 41.0–48.0 mm]; \( P = 0.027 \)) compared with baseline values from the control group (Figure 1). Absolute platelet concentration remained unchanged (221 [standard deviation {SD}]±66) \( 10^9/l \) at 72 h vs. 244 [SD ± 88] \( 10^9/l \) at baseline of the control group; \( P = 0.426 \)). Compared with the aSAH value at 72 hours, EXTEM-CFT decreased significantly from the baseline value of the control group (96.5 s [IQR, 81.3–120.5 s] vs. 74.0 s [65.0–89.0 s]; \( P = 0.015 \)). No differences in INTEM-MCF, EXTEM-CT, INTEM-CT, and INTEM-CFT were observed at 72 hours compared with baseline values from the control group (Table 3). Other time comparisons (12, 24, and 48 hours after onset of aSAH symptoms) to baseline values of the control group are shown in Table 3.

Further, DCI was observed in seven (\( n = 17, 41 \% \)) aSAH patients. At 72 hours, FIBTEM-MCF was significantly higher in patients who developed DCI compared with those who did not (25.0 mm [IQR, 24.8–26.8 mm] vs. 19.0 mm [IQR, 16.5–22.5 mm]; \( P = 0.012 \)) (Figure 2). No differences were detected in EXTEM-MCF (68.5 mm [IQR, 66.8–69.8 mm] vs. 67.0 mm [IQR,
64.5–71.5 mm]; \( P = 0.698 \) or INTEM-MCF (66.0 mm [IQR 36.0–70.5 mm] vs. 68.0 mm [IQR 65.5–71.5 mm]; \( P = 0.606 \)). Four patients had severe EBI, and in these patients, FIBTEM-MCF was significantly higher at 72 hours compared with mild EBI patients (26.0 mm [IQR, 25.0–26.0 mm] vs. 22.0 mm [IQR, 18.3–24.8 mm]; \( P = 0.031 \)) (Figure 2). EXTEM-MCF was unchanged at 72 hours (data not shown).

Two DVTs were detected in aSAH patients, and both patients also developed a PE. In these patients, EXTEM-MCF was not higher compared with other aSAH patients at 72 hours (61.5 mm [IQR, 57.0–61.5 mm] vs. 69.0 mm [IQR, 66.5–71.5 mm]; \( P = 0.076 \)). No thromboembolic complications were observed in the control group.

**DISCUSSION**

This clinical, observational trial examined the on-going coagulation process after aSAH using ROTEM® analysis. We observed that at 72 hours after onset of aSAH, strength of the formed blood clot increased, as shown by higher EXTEM-MCF and FIBTEM-MCF values. Higher FIBTEM-MCF levels were associated with incidence of DCI and EBI. To the best of our knowledge, this is the first time that ROTEM® has been used to examine changes in coagulation after aSAH.
In this study, EXTEM-MCF increased at 72 hours after onset of aSAH, suggesting overall coagulability was increased. In previous trials, haemostatic changes following aSAH have been investigated by another viscoelastic point-of-care coagulation test, thromboelastography (TEG®), in which overall coagulation state is evaluated by maximum amplitude (MA), which is analogous to the MCF value in ROTEM®. The results of these studies are consistent with ours in moderate to severe aSAH patients, with onset of the hypercoagulable state observed at 3 days from bleeding, while MA levels were highest on day 10. When the monitoring period was shorter than 72 hours, no change in MA value was observed in the overall aSAH population. Interpretation of these previous results is difficult, as the exact timing of the blood samples is not known. Moreover, as blood coagulation has been activated by different reagents in previous trials, direct comparison between results is challenging. We chose to use the extrinsic pathway because it most accurately mimics rupture of an aneurysm and release of tissue factors to initiate blood coagulation. However, these data suggest that the hypercoagulation state develops gradually after aSAH and can be detected by viscoelastic point-of-care coagulation test 3 days after bleeding.

We noted that at 72 hours after the onset of aSAH bleeding, FIBTEM-MCF levels significantly increased. This implies that fibrin formation and polymerisation exert a major contribution on clot strength. To the best of our knowledge no previous trials have investigated fibrin function after aSAH. In general, FIBTEM-MCF is a surrogate marker for plasma fibrinogen concentration, and they are both known to increase in the recovery phase of many acute illnesses.
(e.g., severe sepsis). When measured at the early phase of aSAH, fibrinogen concentration is reportedly within normal limits or slightly elevated. However, we have not found any trials where change in fibrinogen concentration had been studied. It is known that higher values of the fibrin degradation product, D-dimer, after aSAH are associated with poor neurological outcome. This is in accordance with our results since a higher D-dimer value implies that fibrin formation is increased, as does higher FIBTEM-MCF. Additional studies are needed to confirm these results and determine if FIBTEM-MCF continues to increase after 3 days.

We noticed that both absolute and relative differences between EXTEM-MCF and FIBTEM-MCF decreased after 72 hours while the absolute platelet concentration remained unchanged. This shows that the functional impact of platelets on formation of clot strength is declining and outlines the functional impact of fibrin. In previous TEG® trials, clot strength was solely evaluated by MA, and thickening of the clot was concluded to reflect activation of platelets only. In a recent trial, activation and aggregation of platelets was observed after aSAH. Nevertheless, it is known that both platelet activation and fibrin formation and crosslinking are needed for clot formation. The relative contribution of platelets and fibrin to clot strength in aSAH patients is unknown. In healthy individuals, fibrinogen accounts for 25% of clot strength while in trauma patients the contribution increases up to 44% after 72 hours of insult. Based on our results, it appears that the relative contribution of fibrinogen also increases after aSAH, from 23.5% to 33.3% at 72 hours after onset of aSAH.
We found significantly higher FIBTEM-MCF at 72 hours in patients who had severe EBI or further developed DCI. Interestingly, we did not observe any association between DCI and EXTEM-MCF though the absolute increase in EXTEM-MCF was statistically significant. To our knowledge no trial has investigated this previously. Fuji et al., found higher fibrinogen levels predicted incidence of DCI at 6 days after aSAH, while baseline fibrinogen concentration has not shown association with poor neurological outcome. Based on previous TEG® trials, association with MA levels and EBI or DCI is inconsistent. Some studies have stated that higher MA levels increase the likelihood of severe EBI and developing DCI, while others did not observe any association with DCI, although hypercoagulability was associated with a poor neurological outcome.

These inconsistent results might be due to the widely varied definitions used for DCI. Moreover, the pathophysiology of DCI is complex and not completely understood. It is known that aneurysm rupture causes platelet activation, which results in thrombin generation, further fibrin cleavage from fibrinogen, and formation of cerebral microthrombi. Ultimately, this may contribute to the pathophysiology of DCI. Based on our results, it seems that increasing fibrin formation and polymerisation might play a role in the pathophysiology of DCI. In clinical setting the antiplatelet therapy has failed to prevent this increased fibrin formation or reduce the incidence of DCI or mortality after aSAH. Nonetheless, a recent retrospective trial showed promising result when dual antiplatelet therapy was used.
Interestingly, overall incidence of VTE in our study was high: 11.8% for both DVT and PE. In previous trials, incidence of DVT among aSAH patients varied between 2 to 24% depending on if a screening method was used.\textsuperscript{37,38} Although there is weak evidence that earlier onset of clot formation might increase risk for DVT,\textsuperscript{23} in our current trial we did not observe shortened EXTEM-CT or elevated EXTEM-MCF among the two VTE patients. Moreover, EXTEM-CT and INTEM-CT remained unchanged during the study period in whole aSAH group indicating that initiation of clotting, thrombin formation, and start of fibrin polymerisation were unaffected. In general the predictive value of TEG for VTE diagnostics is highly inconsistent.\textsuperscript{39} Thus, a much larger trial is needed to show association with changes in coagulation factors and incidence of VTE after aSAH. Altogether, this supports the current practise to start pharmacological thromboprophylaxis as early as is safe.\textsuperscript{15}

This study has limitations. First, there was a 12-hour delay from the onset of initial bleeding to the first ROTEM® measurement. However, this delay is inevitable when performing clinical research on this patient population. Second, we monitored ROTEM® measurements for only 72 hours. In previous TEG® trials, coagulation continued to increase from day 3 to day 10, with a clear hypercoagulability state identified on day 5.\textsuperscript{24} Third, even although neurosurgical patients undergoing elective aneurysmal clipping represent the same patient population, the aSAH patients were younger and proportion of smokers higher. This is unsurprising, since smoking is known to be one of the major risk factors for aneurysm rupture.\textsuperscript{40} Yet, it is not known if smoking affects ROTEM® results. Fourth, decrease in haemoglobin level after aSAH might have
paradoxically increased the measured EXTEM-MCF. However, the magnitude of this is most likely minimal.\textsuperscript{41} and the precision of FIBTEM-MCF measurement is known to be actually better in anaemic patients\textsuperscript{42} Fifth, our sample size was underpowered for some clinical endpoints (e.g., DCI, EBI and VTE), thus these results must be interpreted with caution. Furthermore, due to small sample size we were unable to perform multivariate testing on other clinically relevant confounders, e.g. Hunt Hess or Fisher score, that might have influence on incidence of EBI and DCI. Finally, based on current trial design we were unable to differentiate what is the effect of different operative interventions on blood coagulation.

In conclusion, our study shows that blood coagulation appears to increase at 72 hours after onset of aSAH, and for the first time this change can be detected by ROTEM® EXTEM-MCF analysis. At the same time, FIBTEM-MCF is also elevated, suggesting that relative contribution of fibrin formation and fibrin polymerisation to clot strength are essential. Further, FIBTEM-MCF was higher in patients with DCI and EBI. Thus, it seems that formation and polymerisation of fibrin might influence pathophysiology of DCI and EBI. Further clinical trials are warranted to confirm these results.
Details of authors contributions

A.V: Acquisition, analysis and interpretation of data and preparation of manuscript, E.J: Acquisition, analysis and interpretation of data and review of manuscript, V.J: acquisition of data and review of manuscript, H.H: Statistical analysis of data and review of manuscript, K.K: Acquisition of data and review of manuscript, P.H: Acquisition of data, neurosurgical expertise in data interpretation and review of manuscript, A.K: study conception and design, acquisition of data and review of manuscript.

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Declaration of Interests: none declared.
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FIGURE LEGENDS

Figure 1

Change in ROTEM® analysis from baseline value of the control group to 72 hours after onset of aSAH symptoms.

A. EXTEM-MCF(mm). Baseline median: 64.5 (IQR 59.5–66.8) and at 72 hours: 68.0 (IQR 66.0–71.0); \( P = 0.024 \).

B. FIBTEM-MCF (mm). Baseline median: 15.0 (IQR 12.5–17.8) and at 72 hours: 23.0 (IQR, 19.0–25.0); \( P = 0.001 \).

C. Difference between EXTEM-MCF(mm) and FIBTEM-MCF (mm) represents the impact of platelets on clot formation. Baseline median: 48.5 (IQR, 46.3–50.8) and at 72 hours: 44.0 (IQR, 41.0–48.0); \( P = 0.027 \).

Statistical significance was established at \( P < 0.05 \), marked with ♦ aSAH: aneurysmal subarachnoid haemorrhage.
Association with fibrin formation and polymerisation (FIBTEM-MCF) over 72 hours after onset of aSAH symptoms with incidence of EBI and DCI.

A. In severe EBI patients (n = 4), FIBTEM-MCF(mm) was significantly higher at 72 hours compared with mild EBI patients (26.0 mm [interquartile range {IQR}, 25.0–26.0 mm] vs. 22.0 mm [IQR, 18.3–24.8 mm]); P = 0.031.

B. In DCI patients (n = 7), FIBTEM-MCF(mm) at 72 hours was 25.0 (IQR, 24.8–26.8) compared with 19.0 (IQR 16.5–22.5) for non-DCI patients (n = 10); P = 0.12.

Statistical significance was established at p < 0.05, marked with ♦ aSAH: aneurysmal subarachnoid haemorrhage, EBI: early brain injury, DCI: delayed cerebral ischemia
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Abbreviations: aSAH; aneurysmal subarachnoid haemorrhage, BMI; body mass index, HTA; hypertensio arterialis, ACA; anterior communicating artery, BA; Basilar Artery, ICA; internal carotid artery, MCA; middle cerebral artery, PCA; posterior cerebral artery, PA; pericallosal artery
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<tr>
<td>LMWH during ICU</td>
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<tr>
<td>GOS score at 90 d</td>
<td>6.7 ± 1.9</td>
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<tr>
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Abbreviations: TXA; tranexamic acid, LMWH; low molecular weight heparin, GOS; Glasgow Outcome Score Extended
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<th>Parameter</th>
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<th>Baseline of the control group</th>
<th>From the onset of aSAH (h)</th>
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<td>Median Q₁-Q₃</td>
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<td>Haemoglobin (g/l), mean SD</td>
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<td>CRP (mg/l)</td>
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<td>23.7</td>
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</table>

Table 3
Laboratory Results and ROTEM® Assays

All statistical comparison are done between baseline of the control group and different time point of aSAH group

Abbreviations: aSAH; aneurysmal subarachnoid haemorrhage, MCF; maximum clot firmness, CT; clotting time, CFT; clot formation time, CRP; C-reactive protein

*0.024
†0.023
‡0.015
§0.004
¶0.001
*0.010
*<0.001
**<0.001