Clin. Lab. 2021;67:XXX-XXX
©Copyright

ORIGINAL ARTICLE

Reduced Platelet Activity in Patients with Acute Intracranial Hemorrhage

Hannes Warmuth [1], Kai Zacharowski [2], Volker Seifert [3], Jürgen Konczalla [3], Christian F. Weber [1, 2, *], Haitham Mutlak [2, 4, *]

** C. F. Weber and H. Mutlak contributed equally to this manuscript*
[1] Department of Anesthesiology, Intensive Care and Emergency Medicine, Asklepios Clinics Hamburg, AK Wandsbek, Germany
[2] Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt, Germany
[3] Department of Neurosurgery, University Hospital Frankfurt, Frankfurt, Germany
[4] Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, SANA Clinic Offenbach, Offenbach, Germany

SUMMARY

Background: **Acquired platelet dysfunction is a common element of trauma-induced coagulopathy and has been linked to increased mortality. The aim of the study was to describe the prevalence of platelet dysfunction in patients with acute intracranial bleeding.**
Methods: **Patients diagnosed with acute intracranial bleeding were screened for eligibility. Patients with an urgent need for craniotomy were enrolled in this prospective monocentric study. Platelet function analyses using multiple electrode aggregometry (TRAPtest, ASPItest and ADPtest) and conventional coagulation tests were performed. The area under the aggregation curves of the ASPItest and ADPtest were defined as primary outcome variables.**
Results: **Seventy-seven patients were screened for eligibility, and 49 patients were ultimately enrolled in the study. In 14 patients (29%), clinically relevant platelet dysfunction was observed. Of those, 8 patients were treated with antiaggregatory medication at the time of study inclusion. Six patients (12%) were diagnosed with acute acquired platelet dysfunction.**
Conclusions: **Decreased platelet function was present in nearly one-third of patients with acute intracranial bleeding. Hemotherapy algorithms for the treatment of coagulopathy in this cohort should incorporate aggregometric measures to enable rapid goal-directed therapy.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.201136)

Correspondence:
Christian Friedrich Weber, MD
Asklepios Clinics Hamburg
AK Wandsbek
Alphonsstraße 14
22043 Hamburg
Germany
Phone: +49 40 181883-1267
Fax: +49 40 181883-1270
Email: c.weber@asklepios.com

Manuscript accepted December 2, 2020

KEY WORDS

intracranial hemorrhage, coagulopathy, platelet dysfunction, aggregometry, multiplate

INTRODUCTION

Each year, millions of patients suffer acute intracranial hemorrhage that originates from various causes such as traumatic brain injury, spontaneous intracerebral bleeding, subarachnoid hemorrhage, and isolated intraventricular hemorrhage [1,2]. Morbidity and mortality from intracranial hemorrhage are causally linked to bleeding volume, which depends on the patient's current hemostaseological state [3].
In addition to pre-existing hereditary and acute acquired

disturbances of the hemostatic balance, the intake of anticoagulatory medication promotes bleeding, leads to increased hematoma growth and thereby negatively affects the patient's outcome [4]. In this context, antiplatelet therapy is of high clinical relevance: more than a quarter of patients with intracranial bleeding (ICB) are on ADP antagonists or cyclooxygenase inhibitors, which have been found to double the risk of unfavorable outcomes [5] and to be a significant predictor of increased mortality [6-8]. Even monotherapy with low-dose aspirin represents a relevant risk factor because the aspirin-associated inhibition of platelet arachidonic acid-induced aggregability increases the risk of intracranial hemorrhage [9].

In recent years, scientific progress, particularly in the field of trauma-induced coagulopathy, has led to a more comprehensive understanding of the underlying pathophysiological principles of acute acquired coagulopathy [10]. With regard to disturbances of the primary hemostasis, studies have shown that aggregometric results of the phenomenon known as "early platelet dysfunction" resemble those obtained in patients being effectively treated with antiaggregatory medication; these results present as reduced platelet aggregability following *in vitro* stimulation with arachidonic acid (AA), ADP, collagen, or thrombin [11,12].

Early platelet dysfunction has been studied as a feature of traumatic brain injury and aneurysmal subarachnoid hemorrhage [13,14]. Its occurrence seems to be of high therapeutic and prognostic relevance because reduced platelet aggregability is associated with coagulopathic bleeding and correlated with mortality [14,15].

Knowledge about potential disturbances in primary hemostasis may influence perioperative hemostatic therapy in patients suffering from intracranial hemorrhage. Therefore, the aims of the present study were to characterize early platelet dysfunction and to analyze its prevalence and aggregometric performance in this cohort.

MATERIALS AND METHODS

Trial design

The present monocentric study was conducted at the University Hospital Frankfurt (Germany) in cooperation with the Department of Neurosurgery and the Department of Anesthesiology, Intensive Care Medicine and Pain Therapy. The study complies with the Declaration of Helsinki and was approved by the local Scientific and Ethics Review Board; it was filed under reference number 31513.

Participants

The study sample consisted of patients who were diagnosed with acute intracranial bleeding. Patients were consecutively enrolled in the study if an urgent craniotomy was indicated by the neurosurgeon on duty. Exclusion criteria were defined as hypothermia (< 35°C), younger than 18 years old, pregnancy, absence of written informed consent (obtained from the patients or a legally authorized representative), prevalence of hereditary coagulopathies, platelet count of < 70/nL at the time of admission, and/or exclusive conservative/interventional treatment for the intracranial hemorrhage.

Data collection

As each subject was included in the study, information was recorded on the subject's demographics, anticoagulatory and other long-term medication, clinical characteristics preoperative hematological analysis results were recorded. Intraoperative hemotherapy, the need (and reason) for potential re-operation, and the incidence of non-responsiveness to antiaggregatory medication were monitored.

Hematological Analyses

Blood Sampling

At the time of inclusion in the study, blood was drawn from each patient by cubital vein puncture. For conventional laboratory coagulation analyses, blood was collected in 3-mL tubes containing 0.106 mmol/L sodium citrate as an anticoagulant (Sarstedt AG, Nürnbrecht, Germany) or in 4.7-mL EDTA tubes (Sarstedt AG, Nümbrecht, Germany). For the aggregometric analyses, blood was collected in 2-mL tubes with calcium-balanced heparin as an anticoagulant (PICO 50 arterial blood sampler, Radiometer GmbH, Willich, Germany).

Conventional laboratory coagulation analyses

Conventional laboratory coagulation testing included analyses of platelet count [/nL], international normalized ratio (INR), activated partial prothrombin time [aPTT (sec)], hematocrit [%], and plasma concentration of fibrinogen (mg/d). Analyses were performed at the local chemistry laboratory using fully automated analyzers-specifically, the STA-R Evolution (Roche AG, Grenzach, Germany) and the Sysmex XE 2001 (Sysmex GmbH, Norderstedt, Germany).

Platelet function testing, multiple electrode aggregometry

Aggregometry was performed using multiple electrode aggregometry (MEA) with a Multiplate® analyser (Roche AG, Grenzach-Wyhlen, Germany), located in the intensive care unit of the Department of Neurosurgery. The methodical features of the MEA are based on the impedance aggregometry procedure that was first described by Cardinal and Flower [16].

The MEA enables parallel platelet function testing in up to five preheated (37°C) single-use test cartridges. Saline (300 µL) and heparinized whole blood (300 µL) were added to the test cell. After an incubation period of 3 minutes, blood samples in the cartridges are spiked with 32 µM thrombin receptor-activating peptide (TRAPtest), 0.5 mM arachidonic acid (ASPItest), or 6.4 µM adenosine diphosphate (ADPtest) using commercially available reagents (Roche AG). Activated platelets aggregate at the sensor wires, and the resulting enhance-

ment of the electrical impedance between the sensor wires reflects platelet aggregability. After a test period of 6 minutes, the area under the aggregation curve (AUC) is calculated and quantified as arbitrary aggregation units [U] for each test. The reference ranges for healthy subjects as stated by the manufacturer are 87 - 147 U for the TRAPtest, 51 - 109 U for the ASPItest, and 61 - 96 U for the ADPtest. As previously defined and implemented in several hemotherapy algorithms [17,18], efficient responsiveness to cyclooxygenase inhibitors and ADP antagonists or clinically relevant unspecific platelet dysfunctions are confirmed if the aggregation in the ASPItest and/or ADPtest is lower than 40 U. Standard quality control procedures for each device were routinely performed following the manufacturer's recommendations.

Primary Endpoint

The areas under the aggregation curves following *ex vivo* stimulation of platelet aggregation with arachidonic acid (ASPItest) and ADP (ADPtest) were defined as primary endpoints.

Secondary Endpoints

The secondary variables were as follows:

- The area under the aggregation curve following *ex vivo* stimulation of platelet aggregation with thrombin receptor-activating peptide (TRAPtest)
- Results of conventional coagulation analyses (i.e., platelet count, INR, aPTT, hematocrit and fibrinogen concentration)
- Amount transfused for hemotherapy
- Incidence of re-operation
- Incidence of non-responsiveness to antiaggregatory medication

Sample size analysis

The sample size analysis for this study was based on a comparison of two proportions: iatrogenic and acute acquired platelet dysfunction. Prinz et al. reported that the proportion of patients diagnosed with brain injury and pharmacologically induced platelet dysfunction (mainly due to cyclooxygenase inhibitors and/or ADP antagonists) was 52.4% [19]. Davis et al. reported that the collective incidence of acute acquired platelet dysfunction (arachidonic acid pathway) in patients with traumatic brain injury was 23.9% [14]. Sample size analysis (proportion 1:52%; proportion 2:24%; power: 0.8; $\alpha < 0.05$) revealed that a sample size of at least 46 patients would be needed to detect significant group differences.

Statistics

Statistical analyses were performed using SigmaPlot 12 (Systat Software GmbH, Erkrath, Germany). Proportional data were analyzed using Fisher's exact test. Group differences were analyzed using a parametric test (Student's *t*-test) or a non-parametric test (Mann-Whitney rank sum test) depending on the distribution of the data (Kolmogorov-Smirnov test). Data are given as numbers (percentages), means ± standard deviations, and medians (25th/75th percentiles), as appropriate. The criterion for statistical significance was set to $p < 0.05$.

RESULTS

A total of 77 patients were assessed for eligibility. Of those, 28 patients fulfilled the exclusion criteria, and 49 patients were ultimately enrolled in this prospective study. Baseline sociodemographic and clinical characteristics of the study cohort, including the results of conventional coagulation analyses, are given in Table 1. Figure 1 shows the results of aggregometric platelet function testing. The extent of platelet aggregation following stimulation with thrombin receptor activating peptide-6 (TRAPtest) was consistently within the reference ranges for unaffected aggregability. In contrast, boxplots of aggregability following stimulation with both arachidonic acid (ASPItest) and ADP (ADPtest) include the lower bound of the reference range for unaffected platelet function (40 U) and thus indicate that a number of patients either used antiaggregatory medication or suffered from acquired unspecific platelet dysfunction.

With regard to the results of aggregometric analyses, patients were divided between Group 1 (unaffected platelet function, n = 35, 71%) and Group 2 (platelet dysfunction of any etiology, n = 14, 29%). Table 2 compares the sociodemographic, clinical, and perioperative characteristics of these two groups and presents the prevalence of non-responsiveness to antiaggregatory medication in Group 1.

Out of 14 patients with reduced platelet function at study inclusion, 8 patients (57%) were treated, 7 with aspirin monotherapy and 1 with dual antiplatelet therapy with aspirin and clopidogrel. Six of 14 patients (43%) diagnosed with relevant platelet dysfunction received no antiaggregatory medication. Comparisons of the aggregometric results of these two groups [ASPItest: 31 (22/38) U vs. 22 (14/35), p = 0.282; ADPtest: 51 (37/62) U vs. 47 (32/64) U, p = 0.95] revealed no significant differences (Figure 2).

DISCUSSION

This prospective monocentric study was conducted to characterize platelet function in patients suffering from acute intracranial hemorrhage. Aggregometric analyses revealed that the incidence of acutely acquired platelet dysfunction was more than 12% and that the aggregometric phenotype of this disorder resembled the aggregometric results obtained from patients who were effectively treated with dual antiplatelet therapy. Among those patients, those with acute acquired platelet dysfunction and those who were treated with antiaggregatory medication represented nearly 30% of the study cohort. Apparently, disturbances in primary hemostasis

Table 1. Baseline sociodemographic and clinical characteristics of the study cohort.

Gender [male (%)]	**22 (45)**
Age [years]	**51 ± 34**
BMI [kg/m^2]	**27 ± 6**
Anticoagulatory medication **Aspirin** **ADP antagonists** **Dual antiplatelet therapy** **Direct Xa inhibitors**	**15 (31)** **14 (29)** **2 (4)** **2 (4)** **1 (2)**
Cause of intracranial hemorrhage **Subarachnoid bleeding** **Intracerebral bleeding** **Subdural hematoma** **Ruptured aneurysm** **Other**	 **24 (49)** **8 (16)** **8 (16)** **5 (10)** **4 (8)**
Conventional coagulation analyses **Platelet count [/nL]** **Quick [%]** **aPTT [sec]** **Fibrinogen [mg/dL]**	 **219 ± 48** **97 ± 12** **31 ± 16** **256 ± 61**

BMI - body mass index, ADP - adenosine diphosphate, INR - international normalized ratio, aPTT - activated partial prothrombin time. The data are presented as numbers (%), means ± standard deviations or medians (25th/75th percentiles), as appropriate.

Table 2. Subgroup characteristics.

	Unaffected platelet function Group 1 (n = 35)	**Platelet dysfunction Group 2 (n = 14)**	**p**
Gender, male [%]	**15 (43%)**	**7 (50%)**	**0.892**
Age [years]	**51 (± 34)**	**64 (± 19)**	**0.364**
BMI [kg/m^2]	**28 (± 4)**	**26 (± 8)**	**0.103**
Perioperative blood loss [mL]	**190 (± 330)**	**180 (± 360)**	**0.966**
Transfusion [%] **EC [%]** **FFP [%]** **PC [%]**	**1 (3%)** **1 (3%)** **0 (0%)** **0 (0%)**	**2 (14%)** **1 (7%)** **1 (7%)** **2 (14%)**	**0.193** **0.494** **0.286** **0.077**
Repeat surgery [%]	**17 (49%)**	**9 (64%)**	**0.497**
Non-responsiveness to antiaggregatory medication **Aspirin** **Clopidogrel**	 **6 (17%)** **0 (0%)**		

Comparison of sociodemographic, clinical, and perioperative characteristics of patients with either normal (Group 1) or decreased (Group 2) platelet aggregability according to ex vivo assessment. BMI - body mass index, EC - erythrocyte concentration, FFP - fresh frozen plasma, PC - platelet concentration. Values are given as numbers (percentages) or means (± standard deviations).

are a common characteristic of patients who have been diagnosed with acute intracranial hemorrhage.

The results of the present study are in line with those obtained from patients after severe trauma [10,20,21]. In recent years, acquired platelet dysfunction has been identified as a specific element of trauma-induced coagulopathy. In addition to hypothermia and acidosis, which are well-known causes of reduced platelet adhesion and aggregation, three other factors were determined to be main contributors to disturbances in primary hemostasis: platelet receptor blockade and shedding, direct effects of traumatic brain injury, and intracellular impairment of platelet integrity.

Trauma and hemorrhage lead to an activation of hemostasis that results in increased plasma concentrations of D-dimer and fibrin degradation products, which have

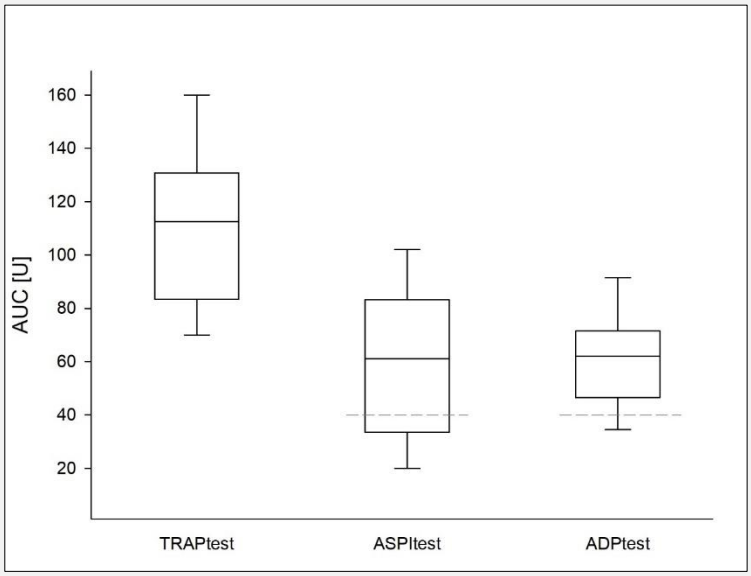

Figure 1.

Figure 1 presents the aggregometric results of the complete study collective following *ex vivo* stimulation of platelet aggregation with thrombin receptor-activating peptide-6 (TRAPtest), arachidonic acid (ASPItest), and ADP (ADPtest). Grey dashed lines indicate an area under the aggregation curve of 40 U, which represents the upper reference value for efficient inhibition of platelet function in the ASPItest and ADPtest.

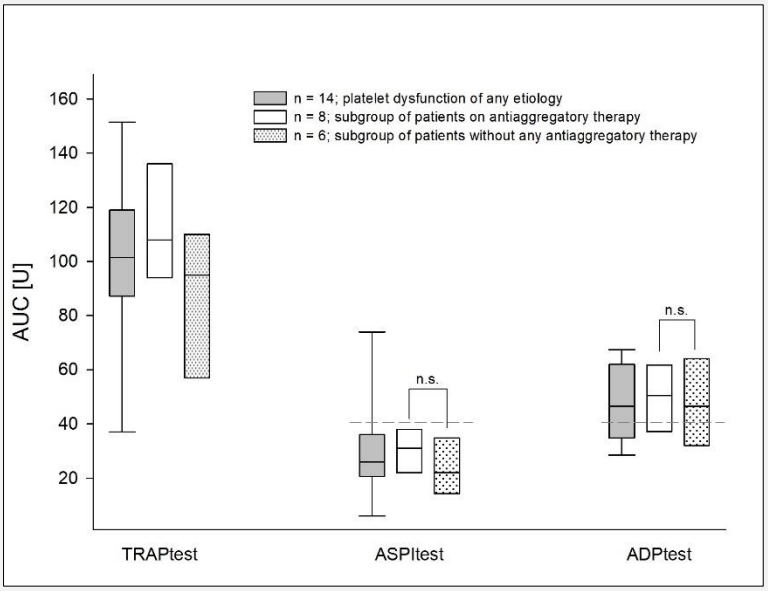

Figure 2.

Figure 2 shows the aggregometric results of a subgroup of patients with reduced platelet aggregability (n = 14), further subdivided into patients with (n = 8) and without (n = 6) antiaggregatory medication at the time of study inclusion. Grey dashed lines indicate an area under the aggregation curve of 40 U, which represents the upper reference value for efficient inhibition of platelet function in the ASPItest and ADPtest. Solid lines represent differences between the indicated groups (n.s. = not significant).

recently been shown to block platelet surface receptors. The resulting impaired platelet signaling process has been associated with coagulopathy, increased blood loss and worsened clinical outcomes [22,23]. Vulliamy et al. showed that trauma patients had a profoundly reduced platelet response to collagen that originated from proteolytic shedding and fragmentation of the platelet collagen receptors glycoprotein (Gp) Ib and Gp VI [24]. Proteolysis is mainly mediated by tissue plasminogen activator (tPA), whose plasma concentration increases depending on endothelial damage and the severity of the trauma. Accordingly, the extent of acquired platelet dysfunction may correlate with both the activation of hemostasis and the severity of trauma. Verni et al. incubated platelets from healthy donors with plasma from trauma patients. In accordance with our results, his aggregometric analyses showed significantly reduced ADP-induced aggregability, indicating that the ADPtest may be the most sensitive test for monitoring acquired platelet dysfunction [25]. Zhao et al. hypothesized that platelet dysfunction may be directly associated with brain injury. They showed that injured brains release cellular microvesicles that induce consumptive coagulopathy and activation of platelets [26,27].

The abovementioned wide spectrum of different triggers for acquired platelet dysfunction limits the diagnostic specificity of reduced aggregometric responses to arachidonic acid (ASPItest) or ADP (ADPtest). In contrast, the ASPItest and ADPtest for the diagnosis of acquired disturbances in primary hemostasis gains diagnostic sensitivity by testing the final pathway of platelet activation, mediated by the Gp IIb/IIIa receptor. For that reason, aggregometry may be a suitable method for rapid assessment of platelet function at the point of care in patients with intracranial hemorrhage.

We did not assess any of the scores that are usually used to reflect the severity and clinical impact of the trauma and intracranial hemorrhage (e.g., Abbreviated Injury Scale and Glasgow Coma Scale scores). We therefore assume that the wide heterogeneity of the relatively small real-life study cohort is the main reason why platelet dysfunction was not associated with poor clinical outcomes as observed in other clinical studies [28]. In addition to the ASPItest and ADPtest, we performed the TRAPtest to analyze the aggregometric response of platelets to stimulation with thrombin receptor activating peptide-6. As expected, the thrombin pathway was too insensitive for monitoring platelet dysfunction; this assay is recommended for the assessment of Gp IIb/IIIa inhibitors or substantial platelet dysfunction that may, for instance, occur in the context of long-term exposure to extracorporeal circulation. The apparent similarity of aggregometric responses in the TRAPtest in the groups with and without acquired platelet dysfunction leads to the suggestion that enzymatic disturbances in the arachidonic acid and thromboxane pathways, along with corresponding dysfunction of the platelet Gp Ib receptor, accounts for the acquired platelet dysfunction observed in 12% of the study cohort. Flow cytometric analyses would have been needed to test this hypothesis. However, the aim of the present study was to analyze only the prevalence and not the etiology of disturbances in the primary hemostasis of patients diagnosed with intracranial bleeding.

A second methodological limitation of this investigation is the lack of baseline and follow-up analyses. It would have been of clinical interest to monitor the duration of decreased platelet dysfunction and the dynamics of potential recovery. In the absence of a control group, we cannot definitively state that the observed effects are "acquired". The comparability of our observations to the reported incidences in other studies corroborates the plausibility of our results [28].

In conclusion, we found a high prevalence of platelet dysfunction in patients diagnosed with intracranial hemorrhage and in need of urgent surgical intervention. Their etiology is approximately half iatrogenic and half acutely acquired. In view of the inability of conventional laboratory coagulation testing to indicate platelet dysfunction, coagulopathic patients may profit from the integration of aggregometric measures into the hemotherapy algorithm.

Sources of Support:
The study was performed without any financial/logistic support.

Declaration of Interest:
Weber CF received speaker honoraria and travel support from CSL Behring, Verum Diagnostica, Hemonetics and Werfen. There were no other conflicts of interest.

References:

1. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018;392:1257-68 (PMID: 30319113).

2. Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. BMC Emerg Med 2009;9:15 (PMID: 19650902).

3. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28:1-5 (PMID: 8996478).

4. Gulati S, Solheim O, Carlsen SM, et al. Risk of intracranial hemorrhage (RICH) in users of oral antithrombotic drugs: Nationwide pharmacoepidemiological study. 2018;13:e0202575 (PMID: 30138389).

5. Fabbri A, Servadei F, Marchesini G. Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study. Crit Care 2013;17:R53 (PMID: 23514619).

6. Roquer J, Rodríguez Campello A, Gomis M, Ois A, Puente V, Munteis E. Munteis. Previous antiplatelet therapy is an independent predictor of 30-day mortality after spontaneous supratentorial intracerebral hemorrhage. J Neurol 2005;252:412-6 (PMID: 15739042).

7. Lovelock CE, Molyneux AJ, Rothwell PM; Oxford Vascular Study. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet Neurol 2007;6:487-93 (PMID: 17509483).

8. Thompson BB, Béjot Y, Caso V, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. Neurology 2010;75:1333-42 (PMID: 20826714).

9. García Rodríguez LA, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanas A. Lanas. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. PLoS One 2016;11:e0160046 (PMID: 27490468).

10. Petros S. Trauma-Induced Coagulopathy. Hamostaseologie 2019;39:20-7 (PMID: 30703820).

11. Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg 2012;214:739-46 (PMID: 22520693).

12. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012;73:13-9 (PMID: 22743367).

13. He Q, Zhou Y, Liu C, et al. Thromboelastography with Platelet Mapping Detects Platelet Dysfunction in Patients with Aneurysmal Subarachnoid Hemorrhage with Rebleeding. Neuropsychiatr Dis Treat 2019;15:3443-51 (PMID: 31908459).

14. Davis PK, Musunuru H, Walsh M, et al. Platelet dysfunction is an early marker for traumatic brain injury-induced coagulopathy. Neurocrit Care 2013;18:201-8 (PMID: 22847397).

15. Castellino FJ, Chapman MP, Donahue DL, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. J Trauma Acute Care Surg 2014;76:1169-76 (PMID: 24747445).

16. Cardinal DC, Flower RJ. The electronic aggregometer: a novel device for assessing platelet behavior in blood. J Pharmacol Methods 1980;3:135-58 (PMID: 7392654).

17. Weber CF, Zacharowski K, Brün K, et al. [Basic algorithm for Point-of-Care based hemotherapy: perioperative treatment of coagulopathic patients]. Anaesthesist 2013;62:464-72 (PMID: 23793973).

18. Weber CF, Zacharowski K, Meybohm P, et al. Hemotherapy al.-gorithms for coagulopathic cardiac surgery patients. Clin Lab 2014;60:1059-63 (PMID: 25016714).

19. Prinz V, Finger T, Bayerl S, et al. High prevalence of pharmacologically induced platelet dysfunction in the acute setting of brain injury. Acta Neurochir (Wien) 2016;158:117-23 (PMID: 26611691).

20. Gratz J, Oberladstätter D, Schöchl H. Trauma-Induced Coagulopathy and Massive Bleeding: Current Hemostatic Concepts and Treatment Strategies. Hamostaseologie 2020 Sep 7 (PMID: 32894876).

21. Vulliamy P, Kornblith LZ, Kutcher ME, Cohen MJ, Brohi K, Neal MD. Alterations in platelet behavior after major trauma: adaptive or maladaptive? Platelets 2020:1-10 (PMID: 31986948).

22. Lee MY, Verni CC, Herbig BA, Diamond SL. Diamond. Soluble fibrin causes an acquired platelet glycoprotein VI signaling defect: implications for coagulopathy. J Thromb Haemost 2017;15:2396-407 (PMID: 28981200).

23. Verni CC, Davila A, Sims CA, Diamond SL. D-Dimer and Fibrin Degradation Products Impair Platelet Signaling: Plasma D-Dimer Is a Predictor and Mediator of Platelet Dysfunction During Trauma. J Appl Lab Med 2020 (PMID: 32674119).

24. Vulliamy P, Montague SJ, Gillespie S, et al. Loss of GPVI and GPIbα contributes to trauma-induced platelet dysfunction in severely injured patients. Blood Adv 2020;4:2623-30 (PMID: 32556282).

25. Verni CC, Davila A Jr, Balian S, Sims CA, Diamond SL. Diamond. Platelet dysfunction during trauma involves diverse signaling pathways and an inhibitory activity in patient-derived plasma. J Trauma Acute Care Surg 2019;86:250-9 (PMID: 30531331).

26. Zhao Z, Zhou Y, Hilton T, et al. Extracellular mitochondria released from traumatized brains induced platelet procoagulant activity. Haematologica 2020;105:209-17 (PMID: 30975909).

27. Zhao Z, Zhou Y, Li M, Zhang J, Dong JF. Dong. Extracellular Mitochondria in Traumatic Brain Injury Induced Coagulopathy. Semin Thromb Hemost 2020;46:167-75 (PMID: 31887759).

28. Kay AB, Morris DS, Collingridge DS, Majercik S. Platelet dysfunction on thromboelastogram is associated with severity of blunt traumatic brain injury. Am J Surg 2019;218:1134-7 (PMID: 31575420).