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Case report | Prikaz slučaja

Traumatic brain injury associated coagulopathy

Koagulopatija kod traumatske ozljede mozga

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Descriptors
COAGULOPATHY; TRAUMATIC BRAIN INJURY; TRAUMA; HAEMORRHAGE

SUMMARY. Traumatic brain injury associated coagulopathy is a widely recognized risk factor for secondary brain damage and a powerful predictor related to outcome and prognosis. It is estimated that two thirds of patients with severe TBI will develop a coagulopathy. Pathophysiological pathway of TBI associated coagulopathy remains poorly defined. It includes combination of hypercoagulable and hypofibrinolytic states that result in persistent and delayed intracranial haemorrhage and systemic bleeding. The proposed mechanisms include release of tissue factor, hyperfibrinolysis, disseminated intravascular coagulopathy, platelet disfunction and protein C activation. The goal of this review is to summarize the current knowledge regarding the mechanisms of traumatic brain injury associated coagulopathy and treatment options.

Deskriptori
KOAGULOPATIJA; TRAUMATSKA OZLJEDA MOZGA; TRAUMA; KRVARENJE

SAŽETAK. Koagulopatije kod traumatske ozljede mozga bitan su faktor u razvoju sekundarnih ozljeda mozga i snažan su prediktor za ishod i prognozu liječenja. Procjenjuje se da dvije trećine pacijenata sa teškom traumom mozga razvije koagulopatiju. Patofiziološki mehanizam koagulopatije kod traumatske ozljede mozga je slabo razjašnjen. Uključuje otpuštanje tkivnog faktora, hiperfibrinolizu, diseminiranu intravaskularnu koagulopatiju, poremećaj funkcije trombocita i aktivaciju proteina C. Cilj ovoga rada je osvrnuti se na aktualna saznanja o patofiziologiji koagulopatije kod traumatske ozljede mozga i metode liječenja.

Trauma is the third leading cause of death in the United States, and it is the leading cause of death in people under the age of 44 (1). Traumatic brain injury (TBI) is a leading cause of trauma related death and disability, and it makes a huge burden on patients, their families and society. Reported incidence rates of TBI across the world vary considerably. It is estimated that 2,5 million new cases of TBI occur in European Union each year (2).

Coagulopathy is the common finding in patients with TBI. The definitions of TBI associated coagulopathy are heterogenous, and they are often based on conventional coagulation assays (CCA) (prothrombin time (PT) with its surrogates, prothrombin ratio and international normalized ratio (INR), activated partial thromboplastin time (APPT)) (3). It manifests as disseminated intracranial haemorrhage, delayed intracranial or intracerebral haematoma, and systemic bleeding (4). The incidence of TBI associated coagulopathy varies from study to study. This variability arises from the inconsistency in the definition of coagulopathy and differences in study design. It is frequently estimated that one third of all patients with TBI, and two thirds of patients with severe TBI will develop a coagulopathy (5,6). Talving and colleagues showed that the Glasgow Coma Score (GCS) ≤8, Injury Severity Score (ISS) ≥16, hypotension upon admission, cerebral oedema, subarachnoid haemorrhage and midline shift are independent risk factors for developing coagulopathy, longer ICU length of stay and an almost 10-fold increased risk of death, in patients with isolated TBI (7). The time interval to coagulopathy onset is also a strong prognostic value. Early coagulopathy occurring 12h after injury, along with markers of devastating head injury, are independent risk factors for mortality (8). Patients on preinjury anticoagulant therapy have twice the risk of expansion of haemorrhagic lesion, delayed intracranial haemorrhage and death (6,9). On the other hand, patients on antiplatelet therapy did not show significant risk of death, compared to a similar cohort of patients without antiplatelet therapy (10).

Pathophysiology

Pathophysiological pathway of TBI associated coagulopathy remains poorly defined and understood (Figure 1.). Coagulopathy associated with extracranial injury is primarily caused by substantial blood loss, consumption, hypothermia, acidosis. On the other hand, patients with isolated TBI do not suffer substantial blood loss, suggesting that TBI associated coagulopathy follows distinct pathogenic pathway (4). The proposed patho-

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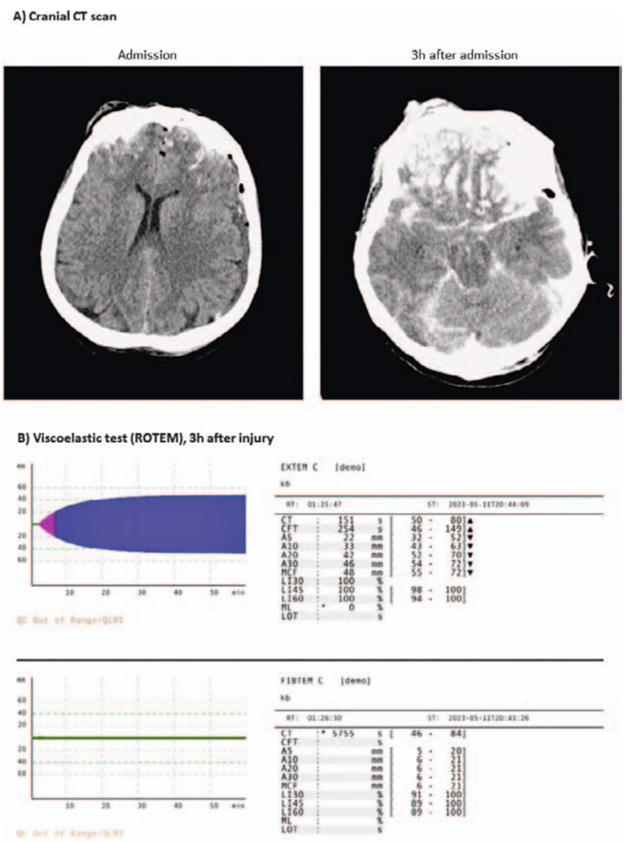

C) Conventional coagulation assays

	Admission	3h interval
PT	81%	41%
INR	1,12	1,83
APTT	29s	45s
Platelet count	160×10⁹/L	130×10⁹/L
Fybrinogen	2,5 g/L	0,6 g/L

FIGURE 1. CLINICAL ASSESSMENT OF PROGRESSION OF TRAUMATIC BRAIN INJURY ASSOCIATED COAGULOPATHY. A 72 YEAR OLD FEMALE PATIENT WITH SEVERE TBI (GCS 8 UPON ADMISSION). (A) CLINICAL CT SCANS SHOW DETERIORATING INTRACRANIAL HAEMORRHAGE. (B) CLINICAL VISCOELASTIC ASSESSMENTS USING ROTEM WAS MADE 3H AFTER ADMISSION. FINDINGS INDICATE DELAYED AND INSUFFICIENT CLOTTING, REFLECTED IN PROLONGED EXTEM CT (151S) AND ABSENT FIBTEM A10. THE FLAT LINE IN FIBTEM CHANNEL REFLECTS THE COMPLETE ABSENCE OF FIBRIN POLYMERISATION. (C) THE RESULT OF CONVENTIONAL COAGULATION ASSAYS CONFIRMS COAGULATION FAILURE AMONG WITH HYPOFIBRINOGENAEMIA.

physiological mechanisms that trigger haemostatic disorders in TBI include platelet disfunction, endogenous anticoagulation, endothelial activation, fibrinogen modifications, inflammation and hyperfibrinolysis (6).

The tissue factor and microparticles

Brain tissue is a rich source of tissue factor (TF). It is primarily expressed on fibroblasts and smooth muscle cells in the vessel wall and non-vascular cells such as astrocytes and epidermal cells (11). TBI and disruption of the blood-brain barrier (BBB) induce a massive realise of TF into systemic circulation, and its binding with fVII, triggering the extrinsic coagulation pathway, with possible platelet depletion and disseminated intravascular coagulation (DIC) (12). DIC can occur within 6h of TBI, resulting in fibrin deposition, microvascular thrombosis and potentially post traumatic cerebral infarction (6).

Some cells, such as platelets and endothelial cells, in response to injury and inflammation, shed membrane and produce small phospholipid vesicles. Those microparticles (MP) carry TF and different proteins specific to their cell of origin. Platelet derived MP contain phosphatidylserine (PS), which can also promote thrombin generation (12). A small French study found a significantly increased levels of procoagulant MP in CSF and peripheral blood on the day of TBI (13). Tian and colleagues tested hypothesis that the brain derived MCs induce a hypercoagulable state and consumptive coagulopathy. They reported that the uninjured mice injected with brain derived MPs developed a hypercoagulable state, measured by prolonged clotting time, fibrinogen depletion and microvascular fibrin deposition in multiple organs (14).

Platelet dysfunction

Platelet dysfunction appears to be major contributor to TBI associated coagulopathy. A platelet count <100,000/mm^3 is associated with a ninefold adjustment risk of death, and a platelet count <175,000/mm^3 is a significant predictor of intracranial haemorrhage progression (15). Platelet depletion without heavy blood loss and microvascular thrombosis might be explained by platelet hyperactivity (16). The mechanism of platelet dysfunction in still unclear. Platelet activating factor (PAF), realised from the neural cells during cerebral ischemia and tissue hypoxia, is a potent platelet agonist. PAF also contributes to BBB breakdown, which realises additional PAF and other brain derived procoagulant molecules (11). Significant platelet disfunction has also been detected in patients with normal platelet count. TBI patients have a dramatically lower platelet response to arachidonic acid (AA), comparing to healthy individuals, which indicates that the platelet disfunction involves the cyclooxygenase pathway as well (17).

Hyperfibrinolysis

Hyperfibrinolysis (HF) represents an additional important confounder to the disturbed coagulation process. It is estimated that 2,5-7% of all trauma patients have present HF in visco-elastic testing, upon emergency room admission (18). Schochl and colleagues, in the study of 33 patients showed that the fulminant, intermediate and late HF result in 100%, 91%, 73% mortality, respectively (19). While some authors propose an overactivation of clotting via TF to be responsible for HF, others suggest that increased levels of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) in TBI patients, increase plasmin, which is the main effector of fibrinolysis (6,12).

Protein C pathway

Shock – trauma induced hypoperfusion with acidosis and high lactate levels may cause the activation of protein C pathway. Protein C inhibits fVa, fVIIIa and plasminogen activator inhibitor-1 (PAI-1), which promotes the further hyperfibrinolysis and inflammation. In the later sequalae, the post-traumatic inflammatory response might result in chronic protein C depletion, which can lead to hypercoagulable state, with susceptibility to infection and thromboembolism (6,12,20).

Treatment options

To date, there are still no specific guidelines for treatment of TBI associated coagulopathy, so the treatment strategies follow those for systemic trauma, except for targeting MAP >80mmHg, and the platelet count >100×10^9/L (6,21). Specific management of coagulopathy is associated with improved mortality and should be implemented immediately upon hospital admission (21,22). The resuscitation measures should be guided by goal directed strategies using conventional coagulation assays and viscoelastic assays rather than empirical administration (21). Below, the current treatment strategies are discussed.

Fresh frozen plasma

The benefit of fresh frozen plasma (FFP) administration in TBI settings is still questioned. Etemadrezaie and colleagues reported a significantly higher mortality rate and increased frequency of delayed traumatic intracerebral haematoma in patients with severe closed head injury threated with empirical infusion of FFP, compared to a similar cohort of patients treated with normal saline (23). On the other hand, two retrospective studies showed a survival benefit of early plasma administration in patients with multifocal intracerebral haematoma (24), or with ratio-based transfusion in patients with isolated TBI (25).

Fibrinogen

Fibrinogen is independent prognostic factor for clinical outcomes in TBI patients. Fibrinogen concentration declines rapidly after TBI, due to increased coagulation factor consumption, and should be kept above 2g/L through administration of fibrinogen concentrate or cryoprecipitate (21,26). In the later stages of TBI, fibrinogen concentration can increase and cause inflammatory responses and increased microvascular permeability (27).

Prothrombin complex concentrate

Prothrombin complex concentrate (PCC) is first choice therapy for emergency reversal of VKA anticoagulant therapy in trauma setting. It is recommended as a primary treatment in patients with life-threatening bleeding and increased INR (21). PCC as an adjunct to FFP decreases the time until craniotomy with faster correction of INR and decreases the need for blood product requirements in patients with TBI (28).

Platelet transfusion

The role of platelet transfusion is still under debate. The platelet count lower than 100×10^9/L is an independent predictor of mortality in TBI. On the other hand platelet disfunction is linked with increased mortality, even in TBI patients with normal platelet count (5). Spinella and colleagues reported an improved 30-day survival for patients with severe TBI, treated with high platelet ratio transfusions (29). The use of platelet transfusion in patients with TBI and preinjury intake of antiplatelet therapy is controversial topic, and there are no adequate evidence to support it (6).

Tranexamic acid

Tranexamic acid (TXA) has become one of the most important therapies in trauma patients. In patients with isolated TBI the risk of exsanguination is low, so the use of TXA in TBI is controversial. The CRASH-3 randomized placebo – controlled trial showed improved outcome in patients with mild and moderate TBI, who received 1g of TXA within 3h of injury, but not in patients with severe TBI (30). Two recent randomized controlled trials examined pre-hospital TXA administration in patients with severe TBI and did not find any difference between the TXA and placebo groups, regarding the mortality or intracerebral haematoma growth (31,32). Bossers and colleagues, in the multicentre controlled study, first demonstrated increased mortality among patients with isolated severe TBI who had received pre-hospital TXA (33).

Conclusion

Coagulopathy is a common finding in patients with TBI and an important independent risk factor related to prognosis. Pathophysiological pathway of TBI associated coagulopathy remains poorly defined and understood. There seems to be hypocoagulative and hypercoagulative states, which can lead to the secondary injury via ischemic or haemorrhagic lesions. The resuscitation measures should be guided by goal directed strategies using conventional coagulation assays and viscoelastic assays rather than empirical administration. There are no strong evidence to support the early administration of TXA in severe TBI setting.

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