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Relationship between tissue perfusion and coagulopathy in traumatic brain injury

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ABSTRACT

Background: Traumatic brain injury (TBI)–related coagulopathy appears to be most prevalent in patients with tissue hypoperfusion, but evidence for this association is scarce. This study investigated the relationship between tissue perfusion and hemostatic derangements in TBI patients.

Materials and methods: Coagulation parameters were measured on emergency department admission in patients with TBI (head abbreviated injury scale $\geq$ 3). The level of hypoperfusion was simultaneously assessed by near-infrared spectroscopy (NIRS) at the forehead and arm, and by base excess and lactate. Coagulopathy was defined as an international normalized ratio $>$ 1.2 and/or activated partial thromboplastin time $>$ 40 s and/or thrombocytopenia ($<120 \times 10^9$/L).

Results: TBI patients with coagulopathy (42%) had more signs of tissue hypoperfusion as indicated by increased lactate levels (2.1 [1.1-3.2] mmol/L *versus* 1.2 [1.0-1.7] mmol/L; $P = 0.017$) and a larger base deficit (−3.0 [−4.6 to −2.0] mmol/L *versus* −0.1 [−2.5 to 1.8] mmol/L; $P < 0.001$). There was no difference in the cerebral or somatic tissue oxygenation index. However, there was a distinct trend toward a moderate inverse association between the cerebral tissue oxygenation index and D-dimer levels (r=−0.40; $P = 0.051$) as marker of fibrinolysis. The presence of coagulopathy was associated with an increased inhospital mortality rate (45.5% *versus* 6.7%; $P = 0.002$).

Conclusions: This is the first study to investigate the relationship between hemostatic derangements and tissue oxygenation using NIRS in TBI patients. This study showed that TBI-related coagulopathy is more profound in patients with metabolic acidosis and increased lactate levels. Although there was no direct relationship between tissue

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oxygenation and coagulopathy, we observed an inverse relationship between NIRS tissue oxygenation levels and fibrinolysis.

Introduction

Traumatic brain injury (TBI) is one of the leading causes of disability, morbidity, and mortality in young adults and has an increasing incidence in the elderly population.[1] A severe, frequently overlooked complication of TBI is the development of coagulopathy, which may additionally contribute to poor outcome.[2-7] We previously showed that approximately 25% of patients with severe isolated TBI are admitted to the emergency department (ED) with signs of coagulopathy, and this number almost doubles in the first 24 h after injury.[4,5] Moreover, coagulopathy is more prevalent in patients with signs of cranial hemorrhage or brain tissue swelling.[6] It is unclear whether TBI-related hemostatic derangements are part of the pathophysiology underlying brain injury, or a manifestation of the impact of brain injury on systemic processes. Recent studies suggest that hemostatic derangements after TBI are the consequence of an imbalance between procoagulant and anticoagulant factors.[7-11] Specifically, activation of the anticoagulant pathway with consequent hyperfibrinolysis may lead to enhanced clot breakdown and bleeding after TBI.[12] Although tissue hypoperfusion caused by brain injury is assumed to be one of the causes of the activation of anticoagulant mechanisms,[13] direct evidence for this etiology is lacking. Brohi *et al.*[11] showed that protein C consumption and higher thrombomodulin levels are associated with indirect signs of tissue hypoperfusion, such as large base deficit, in TBI patients. Lustenberger *et al.*[14] found that patients with isolated TBI-related coagulopathy had higher base deficit and lactate levels than patients without coagulopathy. Although alterations in base deficit point toward tissue hypoperfusion and hypoxia, the literature lacks studies that examine the relationship between alterations in tissue perfusion and oxygenation and the development of coagulation abnormalities. This study investigates the association between tissue hemoglobin oxygenation as measured with near-infrared spectroscopy (NIRS) and acute coagulopathy in TBI patients. NIRS is a noninvasive technique to continuously measure regional tissue hemoglobin saturation (rSO_2).[15,16] In contrast to pulse oximetry, which only measures the arterial component, NIRS captures the arterial, capillary, and venous compartments and reflects the balance between regional oxygen delivery (and hence regional perfusion) and oxygen consumption.[16,17] To our knowledge, this is the first study that examines the role of tissue oxygenation in TBI-related coagulopathy using NIRS. We hypothesize that TBI patients with early signs of coagulopathy show a profound reduction in cerebral and somatic tissue oxygenation when compared with patients without coagulopathy.

Materials and methods

Patient population

The present study was approved by the Institutional Review Board of VU University Medical Center, Amsterdam (NL39832.029.12). The institutional review board waived the need for informed consent. Preliminary inclusion criteria for coagulopathic assessment and NIRS measurements included clinical suspicion of moderate-to-severe TBI. All measurements, as described in detail in the following section, were performed shortly after admission to the ED. The study subsequently restricted inclusion to subjects with a head Abbreviated Injury Scale (head-AIS) of $\geq$3. Exclusion criteria were the use of anticoagulants, prehospital traumatic cardiopulmonary resuscitation, known pregnancy, and age $<$ 18 y.

Monitoring of coagulation and fibrinolysis

Blood samples were immediately drawn after arrival at the ED as part of standard clinical care. Routine screening coagulation tests were performed in the hemostasis laboratory and included activated partial thromboplastin time (aPTT), prothrombin time (prothrombin time with international normalized ratio [INR]), platelet count, hematocrit (Ht), and hemoglobin (Hb). Fibrinogen levels and D-dimers were also routinely measured as markers of clot formation and fibrinolysis.

Rotational thromboelastometry (ROTEM; TEM International, Munich, Germany) was performed to analyze the contact phase of hemostasis (INTEM; activation by ellagic acid), the extrinsic hemostasis system (EXTEM; activation by tissue factor), and the fibrin part of the clot formation (FIBTEM; EXTEM with cytochalasin D to inhibit platelet activation). ROTEM measurement parameters included clotting time, clot formation time, and the alpha angle as markers of clot formation, as well as maximum lysis (ML) as percentage of lost clot firmness over time. Hyperfibrinolysis was defined as an EXTEM ML $>$ 15% within 2 h after initiation of a thromboelastometry measurement.[14] Acute coagulopathy was defined as either an INR $>$ 1.2, or aPTT $>$ 40 s, or thrombocytopenia ($<120 \times 10^9$/L) at ED admission.[4]

Platelet aggregometry

Platelet activity was measured using *in vitro* impedance platelet aggregometry (Chrono-log CH592A whole blood aggregometer; Stago BNL, Leiden, the Netherlands). The Chrono-log device measures platelet function using electrical impedance that is directly related to the level of platelet aggregation to the electrode. Citrated whole blood was preincubated for 10 min at 37°C. After stabilization, 10 μL of 1 mmol/L adenosine diphosphate (ADP; Chrono-log Corporation, Stago BNL, Leiden, the Netherlands) was added as platelet agonist. Platelet activity was measured as the area under the curve, slope, and change in impedance (amplitude, Ω) at 6 min after ADP addition.

Monitoring of cerebral and somatic tissue oxygenation

Systemic parameters for oxygenation and perfusion included arterial pO_2 and pCO_2 pressures, base excess, lactate, and pH.