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Review article

Relationship between trauma-induced coagulopathy and progressive hemorrhagic injury in patients with traumatic brain injury

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ABSTRACT

Progressive hemorrhagic injury (PHI) can be divided into coagulopathy-related PHI and normal coagulation PHI. Coagulation disorders after traumatic brain injuries can be included in trauma-induced coagulopathy (TIC). Some studies showed that TIC is associated with PHI and increases the rates of disability and mortality. In this review, we discussed some mechanisms in TIC, which is of great importance in the development of PHI, including tissue factor (TF) hypothesis, protein C pathway and thrombocytopenia. The main mechanism in the relation of TIC to PHI is hypocoagulability. We also reviewed some coagulopathy parameters and proposed some possible risk factors, predictors and therapies.

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Introduction

Progressive hemorrhagic injury (PHI) is demonstrated to have a high risk of poor outcomes in traumatic brain injury (TBI) patients, including immediate consequences such as death and morbidity, and long-term health disorders.[1,2] To date, A series of studies on the mechanisms of PHI have been made, especially in coagulopathy-related ones. Meanwhile, trauma-induced coagulopathy (TIC) has been discussed in many recent studies, which showed some association with PHI.[3,4] It is important to make these mechanisms clear to provide possible effective clinical interference and to bring better outcomes. Therefore, we reviewed previous studies and recent advances on PHI and TIC, paying special attention to the connection between them, and discuss possible predictors and therapies.

PHI definition and incidence

PHI definition

Since it was first described by Bollinger and co-workers in 1891, secondary intracranial hematomas after head injuries has been referred to by various terms. These terms include delayed traumatic intracerebral hematoma (DTICH), progressive hemorrhagic injury, hemorrhagic progression of contusion (HPC) and hemorrhage progression (HP).[1,5–9] Each definition focus on different molecular mechanisms and progression process. In this review, we use the term PHI to emphasize and clarify: (1) progressive focus on the progression process of hemorrhage in TBI patients, and (2) the new hemorrhage site which is not continuum to the original contusion.

By far, the definition of PHI has not been unified in different studies. Here we define PHI as the appearance of new lesions or a conspicuous increase in the size of brain injury hemorrhagic lesions, i.e. a 25% increase or more in the follow-up CT scans, during the first 24 h or later after impact.[10,11]

PHI incidence and harm

Based on previous studies, the incidence of PHI after moderate and severe TBI varies from 10% to 60%.[11,12] This may be due to different diagnostic criteria and examinations. In a recent study by Yuan and co-workers,[11] the incidence was classified into three groups based on criticality. They set up a scoring system and defined these patients into three risk groups: low risk, intermediate risk and high risk. The PHI rates after TBI for these three groups were 10.3%, 47.3%, and 85.2% in the development cohort, while in the validated cohort, the rates were 10.9%, 47.3% and 86.9%. We recommend this kind of stratified statistics because it

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can provide effective interference suggestions to certain groups of patients.

As a secondary brain injury, PHI brings a high risk of deterioration, morbidity and mortality in TBI patients. A study presented that poor outcomes in patients with PHI is nearly five-fold higher at discharge and four-fold higher after one year than those in patients without PHI.[12] Other risk factors that result in deteriorate outcome in TBI patients include elevated D-dimer level, initial brain contusions size, old age, low GCS score, alcoholism, high copeptin level, coagulopathy, midline shift, contrast extravasation on computed tomographic angiography (CTA), male gender, pupillary reflex abnormalities, head injury severity and hypoperfusion.[4,12–15] Therefore, studies on the mechanism of PHI may provide effective clinical interference and reduce poor outcomes.

Mechanisms of PHI

Mechanism of PHI development

There are three mechanisms explaining the development of PHI. One is the continuous bleeding of microvessels which ruptured at the time of primary injury, or received kinetic energy from the impact that was not sufficient to rupture them, but enough to activate mechanosensitive molecular processes in microvessels, thereby initiating a series of events that will lead to the delayed catastrophic structural failure of microvessels and PHI.[16] Another one is hypocoagulation state after initial hypercoagulopathy.[15] The third one is activated inflammation induced by the release of excitotoxic substances, blood breakdown products and overreaction of clearing tissue debris.[17–20]

Molecular mechanisms

Previous studies have found that PHI might be due to upregulation and activation of sulfonylurea receptor 1 (SUR1)-regulated NCCa-ATP channels in capillary endothelial cells, predisposing to oncotic death of endothelial cells and catastrophic failure of capillary integrity. After kinetic energy compact on microvessels, the SUR1-regulated NCCa-ATP channel can be activated by Sp1 and NF-kB(a mechanosensitive transcription), then is newly upregulated in penumbral capillaries in the region of brain injury, and becomes quite prominent 24 h after injury in both the cortex and the underlying structures deep to the cortical site of impact. Meanwhile, the reduced PHI after blocking SUR1 with glibenclamide or Abcc8-AS confirmed this hypothesis.[6,16] These findings can provide possible targeted therapeutic interference to PHI and bring better outcomes.

TIC definition and mechanisms

Definition and incidence

After severe tissue injury (high injury severity score), there is a traumatic coagulopathy and increased mortality.[15] The definition criteria of TIC varied considerably, which include over 20 different proposed parameters of coagulopathy. These parameters include elevated INR, PT, PTT or D-dimer, decreased fibrinogen or FXIII, higher DIC score, modified DIC score or modified coagulopathy score, lower alpha-2 plasmin inhibitor. Here we cite a table from previous studies which showed various definitions of TIC from 1992 to 2013 (Table 1).[21] The incidence of TIC after TBI ranges widely from 7% to 97.5%, and the mortality of 17%–86%.[3,12,21]

Mechanisms

To date, there are many studies on the mechanisms of TIC, including tissue factor (TF) hypothesis, hyperfibrinolysis, acute coagulopathy of trauma shock (ACoTs) with protein C pathway, thrombocytopenia, and iatrogenic coagulopathy. The iatrogenic coagulopathy hypothesis was recently termed by Cohen.[15] It focus on iatrogenic effects of the beneficial resuscitation practices, in which patients with TBI received massive transfusion and presented with hypothermia, dilution and acidosis, and also decompressive craniectomy can result in tamponade effect, etc. These findings are coherent with previous studies.[12,21] Among these mechanisms, some of them play an important role in the development of PHI.

Relation of TIC to PHI

As mentioned above, TIC is associated with PHI and increases the rates of disability and mortality.[3,4] Yang and co-workers[5] found a high rate (about 55.6%) of TIC among PHI patients. Vice versa, PHI is a major outcome of TIC patients.[10] A study showed 80% of TIC patients developed PHI.[4]

Based on many previous studies, we conclude that the main mechanism in relation of TIC to PHI is hypocoagulability. Here we discuss three mechanisms in TIC which is of great importance in the development of PHI. To make it clear, we use Fig. 1 to present these relations.

Tissue factor (TF) hypothesis

TF (abundant in the brain) is released into the circulation after patients suffering from TBI, then it activate extrinsic pathway and secondary consumption coagulopathy, resulting in hypocoagulability bleeding disorders such as PHI. This process can be represented by the elevation of tissue plasminogenemia activator (tPA), fibrin degradation products, and decrease of depletion of a-2 plasmin inhibitor. However, this hypothesis is challenged by a recent study, which showed similar TF levels in all study groups regardless of the presence of coagulopathy.[3]

Protein C pathway

Protein C can cleave factors Va and VIIa after being activated, and is important for TBI patients survival.[15] ACoTs is defined as APTT and/or INR followed by trauma, shock, and tissue hypoperfusion.[22] Triggered by hypoperfusion and endothelium damage, protein C pathway is over-activated, which then inhibits co-factors Va and VIIa, decreases plasminogen activator inhibitor (PAI-1) levels, increases tPA, leads hyperfibrinolysis and increases D-dimer level.[13,21] These consecutive reactions can decrease coagulability and further may cause PHI.

Thrombocytopenia

Platelet count <175,000 mm^3 was thought to cause a high risk of PHI,[4] while this is proved to have no statistical significance in a recent study.[3] Platelets dysfunction has been shown to be present after TBI, which could contribute to hemorrhagic complications.[23] Therefore, both quantity and quality defects of platelets in TIC can give rise to the development of PHI.

Other coagulopathy parameters

TIC can be recognized by some laboratory tests, which can also indicate possible development of PHI.

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