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Post-isolated Traumatic Brain Injury Systemic Inflammation and Coagulation Dysfunction: Treatment Strategy with Tranexamic Acid Guided by Calgranulin C (S100A12)

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Summary
Traumatic brain injury (TBI) can induce a systemic inflammatory response, which further exacerbates coagulation dysfunction in patients, increasing the risk of cerebral hemorrhage. The key mechanisms underlying coagulation abnormalities after TBI include the activation of tissue plasminogen, hyperactive fibrinolysis, and an imbalance between coagulation and bleeding. Tranexamic acid, as an antifibrinolytic drug, can competitively bind to the lysine binding site of plasmin, thereby inhibiting its fibrinolytic activity. Furthermore, tranexamic acid also possesses anti-inflammatory properties. Plasmin can enhance the inflammatory response by activating pro-inflammatory cells and inducing the expression of inflammation-related genes. Notably, serum levels of calgranulin C (S100A12) are closely associated with the severity of cranial injury, inflammatory responses, and patient prognosis. Therefore, this study aims to explore, through literature review, whether calgranulin C (S100A12) can guide the feasibility of applying tranexamic acid in the treatment of isolated traumatic brain injury.

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I. Introduction

Traumatic Brain Injury (TBI) is a brain injury caused by external mechanical forces, potentially leading to transient or lasting functional impairments. Among them, isolated traumatic brain injury (iTBI) refers to TBI that does not accompany other apparent extracranial injuries. Currently, brain trauma has become a leading cause of death and disability worldwide. Cerebral hemorrhage plays a significant clinical role in TBI, with trauma-induced coagulation disorders being a pivotal factor in its exacerbation[1]. Additionally, cerebral ischemia following cranial injury represents a form of secondary damage, potentially intensifying neurological impairments and raising risks of mortality and disability[2-3]. Systemic inflammatory responses post-brain injury can further aggravate coagulation dysfunctions, serving as one of the crucial factors in secondary brain injury. Research has highlighted that the activation of tissue plasminogen, hyperactive fibrinolysis, and imbalances between coagulation and bleeding are primary mechanisms underlying coagulation abnormalities post-TBI[4]. Severe brain injuries might induce intense stress reactions, subsequently triggering systemic inflammatory response syndrome. This not only can result in exacerbated hemorrhaging, increased transfusion requirements, and multi-organ failure but might also intensify coagulation abnormalities, heightening mortality risks[5]. Tranexamic acid, as an antifibrinolytic agent, can competitively bind to the lysine binding site of plasmin, thereby inhibiting its activity. Moreover, it exhibits anti-inflammatory properties, capable of preventing the inflammatory responses instigated by plasmin through activating pro-inflammatory cells and promoting the expression of inflammation-related genes[6]. Tranexamic acid can interrupt this inflammatory process by inhibiting the conversion from plasminogen to plasmin. Notably, serum levels of S100A12 are tightly associated with the severity of TBI, inflammation, and prognosis, with evidence suggesting that serum S100A12 can serve as a potential biomarker for assessing the clinical prognosis of TBI patients.

1. Coagulation changes associated with isolated traumatic brain injury

Isolated severe traumatic brain injury (iSTBI) is closely associated with early coagulation disorders. In a two-year prospective study, iSTBI patients were screened, defining Acute Traumatic Coagulopathy (TIC) as having an International Normalized Ratio (INR) ≥ 1.27, Prothrombin Time (PT) ≥ 16.7 seconds, or Activated Partial Thromboplastin Time (aPTT) ≥ 28.8 seconds upon admission. Results showed that out of 120 eligible patients, the average age was 35.7±12.12 years, with 96% being male. TIC was detected in 50 (41.6%) of these patients, of which 60% were associated with acidosis. This study concluded that the incidence rate of TIC in iSTBI is 41.6%, associated with a 4.7-fold increase in mortality[7].TBI leads to an enhanced activation of the coagulation mechanism, insufficient inhibition, and excessive generation of thrombin, resulting in increased dissolution of fibrin. It's worth noting that coagulation disorders occurring in TBI patients might coexist with Disseminated Intravascular Coagulation (DIC). In another retrospective study, 92 iTBI patients were divided into DIC and non-DIC groups based on the DIC scoring system of the Japanese Association for Acute Medicine. The study found that compared to non-DIC patients, those with DIC exhibited more severe coagulation disorders, accompanied by systemic inflammatory response, organ dysfunction, and a higher need for blood transfusion, leading to worse clinical outcomes[8].Traumatic Brain Injury (TBI) can lead to a series of coagulation and fibrinolytic anomalies. After the injury, fibrinogen is rapidly consumed and degraded, reaching its lowest concentration typically within 3-6 hours post-injury. This hypercoagulable state leads to an increased fibrinolytic activity, resulting in a rapid rise in D-dimer plasma levels, peaking within 3 hours[9].Recently, data suggests that TBI itself can promote a systemic pro-coagulation state through the release of cerebral extracellular vesicles. In a retrospective study involving 61 TBI patients, researchers measured biochemical markers of coagulation and fibrinolysis at different post-injury time points[10]. The study results indicate that the post-injury hypercoagulation and fibrinolytic states are closely associated with poor prognosis[11].

2.**Tranexamic Acid in Traumatic Brain Injury**

Tranexamic acid (TXA) is an antifibrinolytic drug derived from lysine. It effectively binds to the lysine binding sites of plasminogen, thereby preventing the interaction between fibrin and plasmin by saturating these sites[12]. Although plasmin continues to form, it cannot bind to fibrin or its monomers. Additionally, TXA exhibits distinct anti-inflammatory properties. Plasmin can promote inflammatory responses by activating pro-inflammatory cells and inducing the expression of pro-inflammatory genes. By inhibiting the conversion of plasminogen to plasmin, TXA effectively suppresses this inflammatory activation process[13].In many clinical scenarios, especially in patients undergoing cardiopulmonary bypass and orthopedic joint replacement surgeries, TXA has been shown to be an effective method to reduce systemic inflammation and intraoperative blood loss[14]. As a result, it has been widely used in surgical patients requiring blood transfusion and hemostatic treatments.CRASH-2 is a large randomized controlled trial involving more than 20,000 patients across 40 countries. The study results demonstrated that the use of TXA within the first hour after acute traumatic brain injury can reduce the risk of death due to bleeding by 30%, and the use of TXA within 1-3 hours post-injury can reduce the risk of death by 20%[14]. These findings suggest that TXA might be a promising therapeutic approach for traumatic brain injuries.Lastly, there was a study targeting 100 patients aged between 18-60 years old, with physical conditions ranked as 1 and 2 according to the standards of the American Society of Anesthesiologists. These patients were scheduled for elective craniotomy to remove tumors. Patients received a bolus of 10 mg/kg approximately 20 minutes before skin incision, followed by an infusion of 1 mg/kg/h of TXA or saline. Hemodynamic variables, intravenous fluids, blood loss, and transfusions were measured every 2 hours. Laboratory parameters, such as serum electrolytes and fibrinogen levels, were measured every 3 hours. On postoperative day 5, hemoglobin (Hb) was estimated and estimated blood loss was calculated. Any complications in patients were also monitored. The results showed that, compared to the saline group, the TXA group had a significantly lower average heart rate, higher mean arterial pressure, and higher fibrinogen levels. The TXA group had a lower average total blood loss than the saline group. The transfusion requirements of the two groups were similar. Both groups had comparable EBL and POD5 Hb. The total blood loss in the TXA group was significantly reduced [15].A double-blind, placebo-controlled randomized trial enrolled 238 patients aged 16 and over with moderate to severe TBI (post-resuscitation Glasgow Coma Scale (GCS) of 4 to 12). They underwent a CT brain scan within eight hours of injury and did not have immediate indications for surgery. In addition to other standard treatments, the intervention was a single dose of 2 grams of TXA. The primary outcome was progressive intracranial hemorrhage (PIH), defined as intracranial bleeding not seen on the first CT scan but found on the second, or intracranial bleeding found on the first scan that expanded by 25% or more in any dimension (height, length, or width) on the second scan. The results showed that 21 of the 120 patients assigned to TXA (18%) and 32 of the 118 patients assigned to placebo (27%) had progressive intracranial hemorrhage. There was no evidence that patients assigned to TXA had an increased risk of thromboembolic events. The study concluded that TXA may reduce progressive intracranial bleeding in TBI patients [16].In a randomized trial, 60 adult patients scheduled for elective craniotomy meningioma resection were randomly assigned to receive tranexamic acid (TXA) or a

placebo before the skin incision. Those in the TXA group were first administered an IV push of 20mg/kg over 20 minutes, followed by a continuous infusion at a rate of 1mg/kg/h until the end of surgery. The research team recorded intraoperative blood loss, transfusion requirements, and estimates using a 5-level hemostasis scale. Postoperatively, the tumor resection range and potential complications were observed through CT scans. Compared to the placebo group, the TXA group had significantly reduced blood loss and transfusion needs and performed better on the 5-level hemostasis scale, with the majority of patients demonstrating excellent hemostatic effects[17].A thorough retrospective analysis was conducted on a prospective database from November 2013 to November 2014. All study patients underwent bedside subdural evacuation port system (SEPS) treatment, followed by a daily oral dose of 650mg TXA. Results showed that 20 subdural hematomas in 14 patients met the study criteria. All patients started TXA treatment post-surgery, and during the TXA treatment period, there was no observed increase or delayed recurrence of SDH. In subsequent follow-ups, with one exception, all symptoms were improved. Additionally, no patients presented with venous thrombosis. The study concluded that the volume of chronic SDH decreased by an average of 40.74% after SEPS treatment, and during oral TXA treatment, the residual amount further decreased by 91.31%. No patients experienced delayed recurrence or expansion of SDH[18].An Institutional Review Board-approved retrospective study conducted a continuous analysis of pediatric patients who underwent calvarial vault reconstruction surgery from January 2009 to June 2012[19]. 17 patients who received TXA during surgery were compared with 20 patients who did not receive TXA. The study results indicated that patients in the TXA group had significantly reduced intraoperative blood loss and transfusion volume. Among the patients treated with TXA, no adverse reactions associated with the drug were observed. In conclusion, the use of TXA in pediatric calvarial vault reconstruction surgery significantly reduced perioperative blood loss and transfusion requirements. The administration of TXA is safe and helps to minimize the possibility of adverse reactions associated with transfusions, thus improving patient prognosis[20].

3.Regarding the use of tranexamic acid for isolated traumatic brain injuries, there's ongoing debate

Some studies suggest that tranexamic acid might be associated with risks of cerebral thrombosis and secondary cerebral ischemia[21]. Additionally, it may increase intracranial pressure, leading to intracranial hypoperfusion[22-23], and elevates the risk of microthrombi in the brain[24]. However, other research indicates that tranexamic acid is safe for patients with brain trauma[25-26]. The large-scale multicenter randomized controlled trial, CRASH-3, found that TXA reduces mortality in patients with mild to moderate brain trauma without increasing the risk of thrombosis. Compared to the placebo group, there was no significant difference in the risk of epileptic seizures[27]. A recent meta-analysis reported that TXA might not elevate the risk of adverse events (AEs)[28]. While increasing evidence supports the use of TXA in various surgical settings to reduce bleeding and transfusion rates, postoperative epileptic seizures, one of the main side effects of TXA use, remains a concern in neurosurgery. To ensure the effectiveness and safety in reducing postoperative epileptic seizures, we've opted for a single dose infusion of 20 mg/kg of thrombin A as an intervention[29].

4. **Calgranulin C (S100A12) serves as an independent predictive indicator of functional outcomes in post-brain injury inflammation**

The receptor for advanced glycation end-products (RAGE) has been identified in the central nervous system and is considered a key modulator in inflammation following brain injury[30-32]. S100A12 is the primary pro-inflammatory ligand for RAGE[33-35], suggesting that S100A12 might play a significant role in the inflammation process after brain damage. Recent studies have shown that the concentration of S100A12 in serum is associated with short-term mortality, the severity of the condition, and inflammation after spontaneous cerebral hemorrhage[36]. In patients with acute ischemic stroke, plasma S100A12 has also been recognized as an independent predictor of functional outcomes[37]. A notable increase in the expression of S100A12 mRNA in the peripheral blood of traumatic brain injury patients has been observed[38]. These findings suggest that S100A12 could serve as a biomarker for predicting the prognosis of brain trauma and is related to inflammatory responses.The objective of this study was to explore the relationship between the serum concentration of S100A12 and the 30-day mortality rate in acute cerebral hemorrhage (ICH) patients. A prospective study involved 182 healthy controls and 182 ICH patients. Results indicated that, compared to the control group, there was a significant increase in the concentration of S100A12 in the serum of ICH patients, correlating positively with various factors including the NIHSS score and ICH volume. The study suggests that the concentration of S100A12 could be a critical indicator in predicting the short-term mortality risk of ICH patients[39].Another study examined the association between plasma S100A12 levels and functional outcomes in acute ischemic stroke patients. The results showed a significant correlation between higher concentrations of S100A12 and poor functional outcomes[40].Lastly, a study on traumatic brain injury patients revealed that the concentration of S100A12 in serum correlates with the GCS score upon hospital admission, inflammatory responses, and other vital biomarkers. The conclusion of the research indicates that S100A12 can be considered as a potential biomarker for predicting the clinical prognosis of traumatic brain injury patients[41].

II. Discussion

Traumatic coagulopathy is a major reason for the progressive exacerbation of hemorrhage in isolated traumatic brain injury (iTBI). Systemic inflammatory response following brain injury can further intensify the coagulation dysfunction in patients with brain injury, becoming one of the significant causes for secondary brain injury. The activation of tissue plasminogen, hyperfibrinolysis, and the imbalance between coagulation and bleeding are the principal mechanisms behind post-injury coagulation abnormalities. After a brain injury, a pronounced stress response ensues, triggering systemic inflammatory response syndrome, leading to increased bleeding, greater transfusion needs, systemic organ failure, and further aggravating the patient's coagulation dysfunction. This, in turn, elevates the mortality rate. Tranexamic acid is an antifibrinolytic drug that competitively binds to the lysine binding sites of plasminogen, inhibiting the fibrinolytic activity of plasmin. On the other hand, it has anti-inflammatory properties. Plasmin activates pro-inflammatory cells and upregulates a series of inflammatory responses by inducing pro-inflammatory gene expression. Meanwhile, by inhibiting the conversion of plasminogen to plasmin, it interrupts this inflammation. Serum levels of S100A12 are closely related to the severity of traumatic brain injury, inflammatory response, and prognosis. It has been proven that serum S100A2 can serve as a potential biomarker for the clinical prognosis of traumatic brain injury patients. Therefore, using Calgranulin C (S100A12) to guide the early administration of tranexamic acid for antifibrinolytic therapy in isolated traumatic brain injury is feasible. However, the specific relationship needs further exploration.

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