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Neurointensive Care of Traumatic Brain Injury Patients Based on Coagulation and Fibrinolytic Parameter Monitoring

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Abstract

Coagulopathy, a common complication of traumatic brain injury (TBI), is characterized by a hypercoagulable state developing immediately after injury, with hyperfibrinolysis and bleeding tendency peaking 3 h after injury, followed by fibrinolysis shutdown. Reflecting this timeframe, the coagulation factor fibrinogen is first consumed and then degraded after TBI, its concentration rapidly decreasing by 3 h post-TBI. The fibrinolytic marker D-dimer reaches its maximum concentration at the same time. Hyperfibrinolysis in the acute phase of TBI is associated with poor prognosis via hematoma expansion. In the acute phase, the coagulation and fibrinolysis parameters must be monitored to determine the treatment strategy. The combination of D-dimer plasma level at admission and the level of consciousness upon arrival at the hospital can be used to predict the patients who will "talk and deteriorate." Fibrinogen and D-dimer levels should determine case selection and the amount of fresh frozen plasma required for transfusion. Surgery around 3 h after injury, when fibrinolysis and bleeding diathesis peak, should be avoided if possible. In recent years, attempts have been made to estimate the time of injury from the time course of coagulation and fibrinolysis parameter levels, which has been particularly useful in some cases of pediatric abusive head trauma patients.

Keywords: traumatic brain injury, blood coagulation disorders, treatment, blood transfusion, surgery

Introduction

Traumatic brain injury (TBI) is associated with disruption of coagulation and fibrinolysis.[1-4] A meta-analysis found that 32.7%-35.2% of TBI patients had disordered coagulation and fibrinolysis, which correlated with poor prognosis.[1,2] A German trauma registry study of patients with isolated TBI also found that 22.7% had coagulation and fibrinolytic abnormalities, which correlated with mortality.[4] In healthy individuals, the balance between coagulation and anticoagulation and fibrinolysis and antifibrinolysis is maintained, but trauma disrupts this balance, especially that of the fibrinolytic system, resulting in a bleeding tendency. This response is known to be particularly strong in TBI and is not seen in non-traumatic cerebral hemorrhage. Thus, understanding coagulation and fibrinolysis is essential in TBI, and thus the 4th edition of the Japanese guidelines for the treatment and management of head in-

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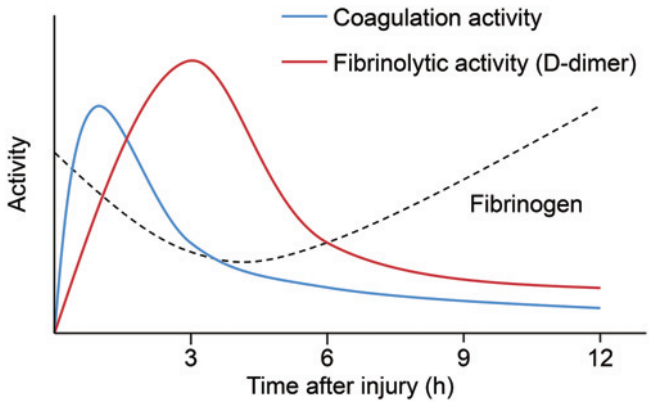

Fig. 1 Schematic diagram of the time course of fibrinolytic and coagulation parameters in traumatic brain injury. This figure is reproduced with the permission from the publisher of Araki T, Yokota H: Letter to the editor. Estimation of date and time of injury using coagulation and fibrinolytic parameters. *J Neurosurg Pediatr* (in press)[37].

jury[5] includes a new section on coagulation and fibrinolysis disorders associated with TBI.

This article reviews the time course of coagulation and fibrinolytic parameters in TBI and its neurointensive care based on the monitoring of these parameters.

Time Course of Coagulopathy in the Acute Phase of TBI

Coagulopathy associated with TBI is characterized by hypercoagulation immediately after injury, hyperfibrinolysis peaking at 3 h after injury, and subsequent fibrinolysis shutdown (Fig. 1). In particular, it is characterized by hyperfibrinolysis resulting in a bleeding tendency (disseminated intravascular coagulation with the fibrinolytic phenotype).[6] We assessed the time course of coagulation and fibrinolytic parameters, including thrombin-antithrombin III complex (TAT), fibrinogen, D-dimer, and plasminogen activator inhibitor-1 (PAI-1), during the acute phase of isolated TBI in patients with Abbreviated Injury Scale (AIS)[7] scores of 3 or above on admission (within 1 h after injury) and at 3, 6, and 12 h after injury (Nippon Medical School Institutional Review Board approval number: #M-2021-025).

Hypercoagulation immediately after TBI

TAT (normal value: <3 ng/mL) is a 1:1 complex of thrombin and its representative inhibitor, antithrombin, and is a marker that reflects the coagulation system. Reflecting the activation of the coagulation pathway and increased thrombin production immediately after TBI, TAT is already abnormally high on arrival at the hospital and decreases 6 h after injury (Fig. 2A). Fibrinogen (normal value: 200-400 mg/dL) is a coagulation factor that plays a central role in hemostasis and is converted to fibrin by thrombin in the final phase of blood clotting. It declines rapidly from arrival at the hospital until 3 h after injury, indicating its consumption and degradation during that time period (Fig. 2B).[8] This trend has been found to be more pronounced in elderly patients.[9]

Hyperfibrinolysis peaking 3 h after TBI

After TBI, the fibrinolytic pathway is activated following the upregulation of the coagulation pathway. D-dimer (normal value: < 1.0 μg/mL) is a fibrin degradation product and a sensitive quantitative marker of the fibrinolytic system. It is already abnormally high on arrival at the hospital in most cases, peaking 3 h after injury and declining thereafter (Fig. 2C).[8] Hyperfibrinolysis is thought to reflect the pathophysiology of the bleeding tendency in TBI, and the D-dimer trend indicates that the bleeding tendency peaks 3 h after injury. This is why craniotomies performed within 3 h of injury are sometimes associated with difficulties in controlling bleeding and continuing the surgery. It has also been found that this occurs in pediatric patients,[10] but is more pronounced in elderly patients.[9]

Subsequent shutdown of fibrinolysis

PAI-1 (normal value: ≤ 50 ng/mL) is a marker reflecting fibrinolysis shutdown; it inhibits plasminogen activators that activate the fibrinolytic pathway. It is elevated from arrival at the hospital, peaks 6 h after injury, and then declines (Fig. 2D). This means that after TBI, the coagulation system, and then the fibrinolytic system, are enhanced, but 6 h after injury, the system switches to fibrinolysis shutdown.

Relationship among Coagulation and Fibrinolytic Parameters, Hemorrhagic Progression, and Outcomes

It has been reported that approximately 50% of TBI patients with coagulopathy have hemorrhagic progression of their first cerebral contusion or intracerebral hematoma within the first few hours after TBI.[11,12] A prospective study by Juratli et al.[11] showed that the incidence of coagulopathy in TBI patients was 47.1% and early hemorrhagic progression of cerebral contusion within the first 6 h was 43.5%. In a retrospective study by Tian et al.,[12] the second computed tomography (CT) scan (mean of 8.8 h after the initial scan) revealed 41.8% of TBI patients to have hemorrhagic progression of injury, with associated elevation of fibrinolytic parameters. Hemorrhagic progression led to later development of non-continuous hemorrhagic lesions and enlargement of preexisting contusions.[13,14]

It has been previously reported that abnormalities in select parameters, including platelet count, prothrombin time (PT), active partial thromboplastin time (APTT), and fibrinogen, fibrinogen/fibrin degradation product (FDP), and D-dimer levels are predictors of poor prognosis in TBI patients.[15-18] However, although coagulation and fibrinolytic

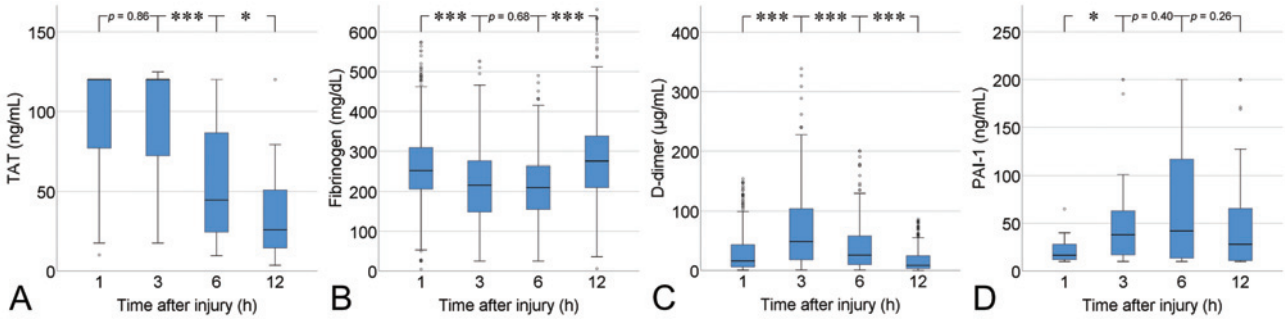

Fig. 2 Time course of coagulation and fibrinolytic parameters after traumatic brain injury (TBI). (A) Time course of plasma levels of thrombin-antithrombin III complex (TAT) at admission and 3, 6, and 12 h after TBI. (B) Time course of fibrinogen plasma levels at admission and 3, 6, and 12 h after TBI. (C) Time course of D-dimer plasma levels at admission and 3, 6, and 12 h after traumatic brain injury. (D) Time course of plasminogen activator inhibitor-1 (PAI-1) plasma levels at admission and 3, 6, and 12 h after TBI. *$p < 0.05$, ***$p < 0.001$. (B, C) Original figures reproduced with the permission from the publisher with a much larger number of cases added based on our previous paper [Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H: Time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury. *J Neurotrauma* 33: 688–695, 2016[8]].

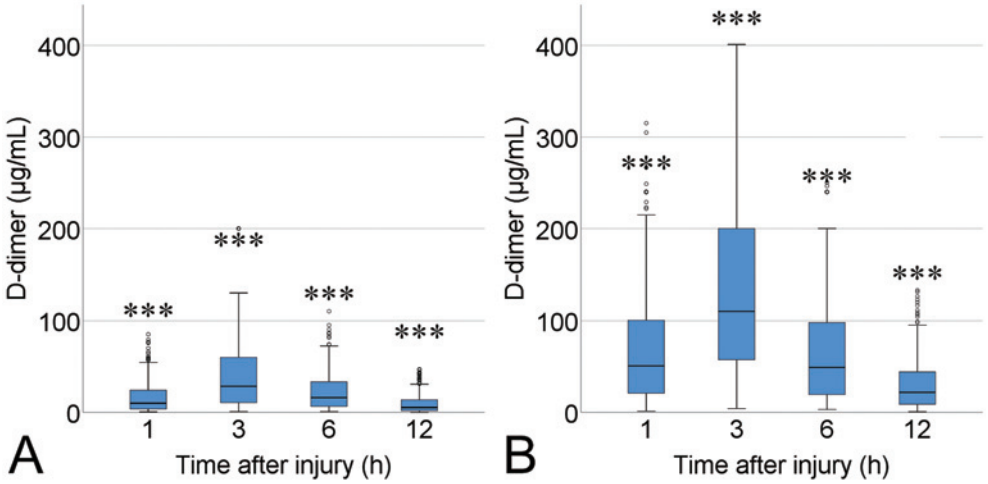

Fig. 3 Time course of D-dimer plasma levels in cases with good (A) or poor (B) outcomes on admission and 3, 6, and 12 h after traumatic brain injury. ***$p < 0.001$. This is the original figure reproduced with the permission from the publisher with a much larger number of cases added based on our previous paper [Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H: Time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury. *J Neurotrauma* 33: 688–695, 2016[8]].

parameters change during the acute phase of TBI, most studies have reported a combination of early and delayed coagulopathy.[19] We compared the D-dimer time course after TBI between the cases with good (Glasgow Outcome Scale [GOS][20]: good recovery [GR]/moderate disability [MD] at 3 months after injury) and poor (GOS: severe disability [SD]/vegetative state [VS]/death [D] at 3 months after injury) outcomes and found that it was significantly higher in the poor than in the good outcome cases from admission to 3, 6, and 12 h after injury (Fig. 3).[8] To determine prognostic factors at hospital arrival, multivariate analysis was performed using age, gender, Glasgow Coma Scale (GCS) score at arrival, AIS-head, type of head injury (e.g., acute subdural hematoma, acute epidural hematoma, cerebral contusion, traumatic subarachnoid hemorrhage), and coagulation fibrinolysis parameters (PT, APTT, fibrinogen, D-dimer) as explanatory variables and patient outcome as response variables. This revealed that D-dimer, in addition to age (threshold value: 58 years) and GCS score (threshold value: 9), were independent predictors of poor prognosis. The D-dimer threshold value that separated survival from death was reported to be 50 μg/mL,[21] and that separated GOS of GR/MD and SD/VS/D in GOS 3 months after injury was reported to be 32.7 μg/mL,[8] suggesting that hyperfibrinolysis in the acute phase of injury is associated with a poor prognosis due to expansion of hematoma.

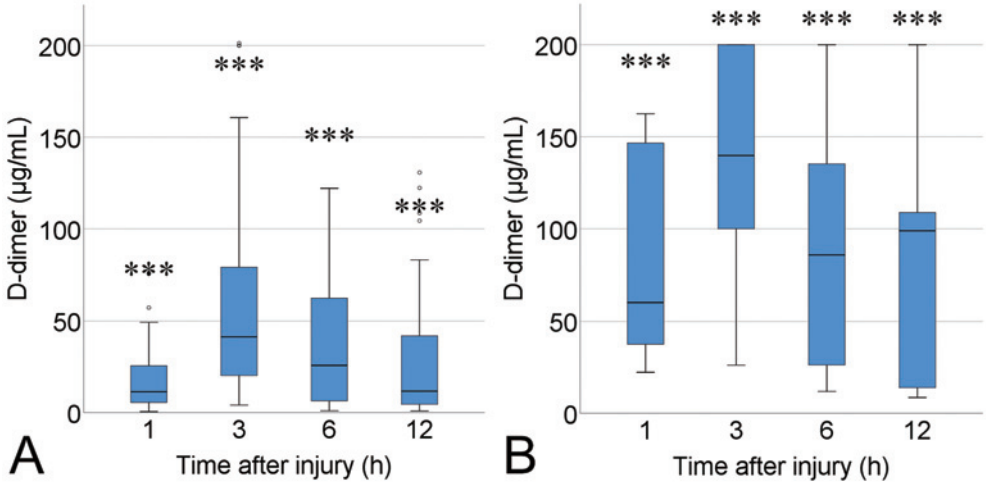

Fig. 4 Time course of D-dimer plasma levels in patients with "non-talk and deteriorate" (A) or "talk and deteriorate" (B) at admission and 3, 6, and 12 h after traumatic brain injury. ***$p < 0.001$. This figure is reproduced with the permission from the publisher of our previous paper [Nakae R, Takayama Y, Ogawa F, Naoe Y, Yokota H: D-dimer as a prognostic marker for head injury patients who talk and deteriorate. *J Jpn Assoc Acute Med* 25: 247–253, 2014 (Japanese)[23]].

Neurointensive Care Based on Monitoring of Coagulation and Fibrinolytic Parameters

In the acute phase of TBI, the balance between coagulation and fibrinolysis is disrupted and the pathophysiology changes dynamically, so it is important to monitor coagulation and fibrinolytic parameters to determine a treatment plan. TBI management and treatment based on coagulation and fibrinolytic parameters include the following.

Predictions for "talk and deteriorate"

Some TBI patients may be able to talk on admission but develop a rapidly progressive loss of consciousness after a short period of time. This condition, termed "talk and deteriorate" (T&D), has a poor prognosis.[22] It is difficult to predict its occurrence at admission. For patients with GCS scores of 13 or higher at admission and D-dimer measured within 1 h after injury, we compared the time courses of the D-dimer levels at admission and 3, 6, and 12 h after injury between patients with (T&D group) and without (non-T&D group) T&D.[23] The D-dimer levels were significantly higher in the T&D group than in the non-T&D group at all-time points (Fig. 4). Plasma D-dimer level on admission was an independent prognostic indicator of T&D, with a threshold value of 37.5 μg/mL. It is worth noting that this threshold value is almost the same as that for GOS divided by GR/MD or SD/VS/D 3 months after injury. Patients with a high level of D-dimer at admission despite a good level of consciousness are more likely to develop T&D, suggesting that the timing of brain CT scan reexamination and surgical intervention should be accelerated.

Fresh frozen plasma transfusion

Trauma patients with heavy bleeding have decreased fibrinogen levels in the early posttraumatic phase.[24,25] Fibrinogen is important for clot firmness.[26,27] It is generally recognized that immediate coagulation factor replacement by fresh frozen plasma (FFP) transfusion, as well as red blood cell transfusion, is associated with improved prognosis in patients with massive extracranial hemorrhage.[28,29] On the other hand, in TBI, the effectiveness of FFP transfusion is not clear, and there are many reports of it being ineffective.[30-33] A matched cohort study of TBI patients found that cases with a poor outcome or death had received more perioperative FFP transfusions than those with good outcome.[33] The complication rates of acute respiratory distress syndrome and pneumonia were significantly higher in patients receiving FFP transfusions than in those who did not. Though the purpose of FFP transfusion is fibrinogen replenishment, these studies did not measure the changes in fibrinogen levels during transfusion. In TBI patients, fibrinogen is rapidly consumed and degraded, suggesting the need for monitoring coagulation and fibrinolytic parameters during FFP transfusion.[3,34] Because the risk of perioperative bleeding complications in non-traumatic diseases is higher at fibrinogen concentrations <150-200 mg/dL, this level is used as an indication for administration of FFP, cryoprecipitate, and fibrinogen concentrate in trauma patients.[29] In a retrospective study of patients with isolated TBI in which plasma fibrinogen concentrations were followed closely, we reported that a fibrinogen concentration of >150 mg/dL at 3 h after injury in patients receiving fibrinogen was associated with a favorable outcome.[34] We also found that the plasma D-dimer level at admission was significantly associated with a decrease in the fibrinogen levels between admission and 3 h

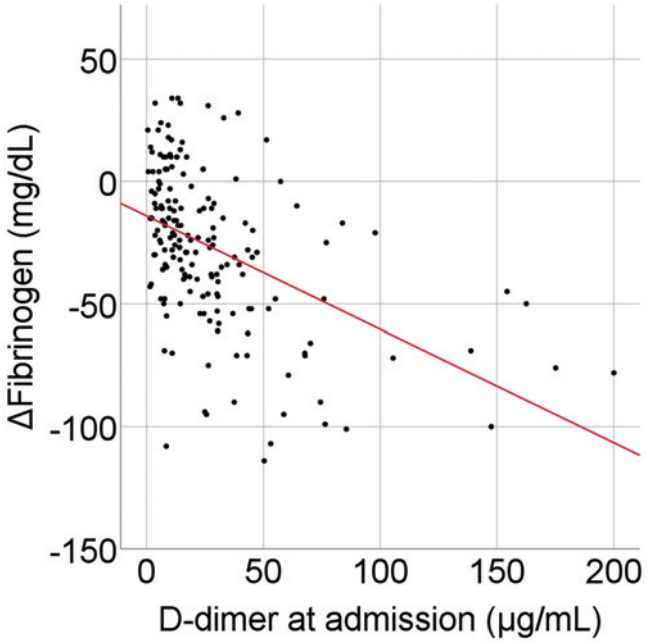

Fig. 5 Correlation between D-dimer and fibrinogen levels from admission to 3 h after traumatic brain injury. ΔFibrinogen = fibrinogen at 3 h – fibrinogen at admission. This figure is reproduced with the permission from the publisher of our previous paper [Nakae R, Yokobori S, Takayama Y, et al.: A retrospective study of the effect of fibrinogen levels during fresh frozen plasma transfusion in patients with traumatic brain injury. *Acta Neurochir (Wien)* 161: 1943–1953, 2019[34]].

post-injury (Fig. 5). FFP transfusion should be considered in patients with low fibrinogen levels on admission, as well as in those with plasma fibrinogen levels in the normal range and high D-dimer levels on admission, as fibrinogen levels subsequently decline significantly in this cohort. The levels of fibrinogen need to be closely monitored during FFP transfusion, as elevated fibrinogen levels due to excessive FFP administration have been reported to induce increased cerebrovascular permeability, which is a risk factor for secondary inflammatory brain injury.[35] It is also important that FFP transfusions be administered in the hyperacute phase within 3 h of injury, as fibrinogen is rapidly consumed and degraded by 3 h after injury, but shifts to fibrinolysis shutdown by 6 h after injury.

Surgery

There is still controversy regarding the optimal treatment for intracranial hemorrhage associated with coagulopathy, including subdural, epidural, and intracranial hematoma. There are several invasive options, including craniotomy, burr hole surgery, ventricular drainage, and intracranial pressure monitoring, but whether such procedures improve the long-term outcome is uncertain. When craniotomy is performed soon after TBI, severe intraoperative bleeding is common due to hyperfibrinolysis, which further decreases coagulation factors and increases the fibrinolytic activity, making hemostasis more difficult. This phenomenon is enhanced within 3 h of injury, when the D-dimer level peaks, and is more significant in severe TBI and TBI with multiple trauma. Kiyohira et al.[36] reported that elective craniotomy for severe subdural hematoma after burr hole surgery and correction of coagulopathy under intracranial pressure (ICP) monitoring did not prolong PT or APTT, reduced transfusion volume, and resulted in better prognosis. To manage ICP immediately after injury, burr hole surgery, which is less likely to affect or be affected by coagulopathy, such as ventricular drainage or hematoma removal through a burr hole, may be effective in the acute phase of TBI. When ICP is high, even slight cerebrospinal fluid drainage significantly reduces ICP (Supplementary Movie 1).

Estimation of time of TBI with coagulation and fibrinolytic parameter levels

In the examination of children, especially infants, the exact time of injury may be unclear due to communication difficulties. In addition, the exact time of injury might also be difficult to determine in cases of abusive head trauma in a medicolegal setting due to possible ambiguities in the alleged perpetrator's testimony and the difficulty in obtaining third-party eyewitness testimony. We found that in pediatric TBI patients, as in adult TBI patients, plasma fibrinogen levels decrease immediately after injury and reach a minimum at 3 to 6 h after injury, while plasma D-dimer levels increase immediately after injury, peaking at 3 h after injury.[10] Accordingly, it might be possible to retrospectively estimate the time of TBI in some patients using the two parameters that exhibit different dynamics, fibrinogen and D-dimer levels, measured at a certain point after arrival at the hospital.[37] Since these markers tend to show a steady transition, there are high expectations for their practical potential as a clinical tool for overall judgment to estimate the timing of injury, and some have been applied in investigations, especially in unwitnessed trauma and abusive head trauma. The estimation of the date and time of injury can be extremely useful in routine clinical settings for determining preoperative hyperfibrinolysis, warning of intraoperative hemostatic maneuvers, and prompt administration of transfusion therapy, as well as in medicolegal settings. However, it is not a definitive judgmental complement, and further research is needed to determine the timing of injury since multiple factors need to be considered.

Conclusion

In the acute phase of TBI, coagulation and fibrinolysis change dynamically. Routine measurement of coagulation and fibrinolytic parameters, including fibrinogen and D-dimer levels, is necessary to predict the onset of coagulo-

pathy and the expected outcome. Monitoring of these parameters is essential in the treatment of TBI.

Supplementary Material

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Abbreviations

AIS = Abbreviated Injury Scale
APTT = active partial thromboplastin time
FFP = fresh frozen plasma
GOS = Glasgow Outcome Scale
GR/MD = good recovery/moderate disability
GCS = Glasgow Coma Scale
ICP = intracranial pressure
PAI-1 = plasminogen activator inhibitor-1
PT = prothrombin time
SD/VS/D = severe disability/vegetative state/death
TAT = thrombin-antithrombin III complex
TBI = traumatic brain injury
T&D = talk and deteriorate

Conflicts of Interest Disclosure

All authors declare that there are no conflicts of interest (COIs) regarding this article according to the criteria of the Japan Neurosurgical Society. Our self-reported registration of our COI status has been submitted to the society.

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