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Case report | Prikaz slučaja

Anticoagulation in patients with traumatic brain injury

Antikoagulacija kod bolesnika s traumatskom ozljedom mozga

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Descriptors
TRAUMATIC BRAIN INJURY;
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INTRACRANIAL HEMORRHAGE PROGRESSION

SUMMARY. The incidence of venous thromboembolic events in trauma patients is highest during the first few days following hospitalization, and traumatic brain injury (TBI) represents an independent risk factor for venous thromboembolism (VTE). Up to 58% of patients with TBI may develop VTE in the absence of any form of prophylaxis and up to 30% with only mechanical prophylaxis. The time to resume or initiate pharmacological thromboprophylaxis (PTP) following TBI is controversial and depends on the evolution of intracranial hematoma on the follow-up head CT scan and the risk of further progression of hematoma. Spontaneous progression of hematoma (without PTP) was seen in 5 – 32% of patients, predominantly in patients with intraparenchymal contusion or intraventricular hemorrhage. In patients with stable intracranial hematoma on follow-up head CT scan PTP should be started within 24–48h, whereas therapeutic doses of anticoagulant drugs should be delayed for at least 12 days. The initiation of PTP during the first 3 days after the urgent surgical intervention is associated with increased risk of repeated neurosurgery, and is therefore not advised. The use of low molecular weight heparin has been associated with lower rates of heparin-induced thrombocytopenia, intracranial hematoma expansion and lower incidence of VTE compared to unfractionated heparin. Prophylaxis with unfractionated heparin may be the preferred agent in high-risk patients with expanding hemorrhagic TBI lesions. Because of low quality of data in the literature guidelines regarding the optimal time to PTP, agent and dose remain vague.

Deskriptori
OZLJEDA MOZGA;
FARMAKOLOŠKA TROMBOPROFILAKSA;
ANTIKOAGULACIJSKA TERAPIJA;
VENSKA TROMBOZA;
INTRAKRANIJALNO KRVARENJE

SAŽETAK. Učestalost venske tromboembolije (VTE) kod pacijenata s traumatskim ozljedama najveća je tijekom prvih dana hospitalizacije, pri čemu traumatska ozljeda mozga (TBI) predstavlja neovisni čimbenik rizika za razvoj VTE. Kod bolesnika s TBI se u nedostatku profilakse VTE može razviti u 58% slučajeva, dok se primjenom samo mehaničke profilakse incidencija razvoja VTE spušta na 30%. Vrijeme za uvođenje farmakološke tromboprofilakse (PTP) nakon TBI je kontroverzno te ovisi o evoluciji intrakranijalnog hematoma na kontrolnom CT-u glave i riziku njegove daljnje progresije. Spontana progresija hematoma (bez PTP) uočena je u 5 – 32% bolesnika, većinom onih s intraparenhimskom kontuzijom ili intraventrikularnim krvarenjem. Kod bolesnika sa stabilnim intrakranijalnim hematomom na kontrolnom CT-u glave PTP treba započeti unutar 24 – 48 sati, dok terapijske doze antikoagulantnih lijekova treba odgoditi za najmanje 12 dana. Početak PTP-a tijekom prva tri dana nakon hitne kirurške intervencije povezan je s povećanim rizikom od ponovnog neurokirurškog zahvata, te se stoga ne savjetuje. Primjena heparina niske molekularne težine povezana je s nižim stopama trombocitopenije izazvane heparinom, širenjem intrakranijalnog hematoma i manjom incidencijom VTE u usporedbi s nefrakcioniranim heparinom. Profilaksa nefrakcioniranim heparinom može biti preferirano sredstvo kod visokorizičnih bolesnika s ekspandirajućim hemoragičnim TBI lezijama. Zbog nedostatnih pouzdanih literaturnih podataka, smjernice o optimalnom vremenu do PTP-a, agensu i dozi ostaju nejasne.

Among all injured patients, the prevalence of traumatic brain injury (TBI) is approximately 20% (1). Venous thromboembolism (VTE) has long been recognized as a common complication in patients with TBI. Lack of mobility and delay to administration of pharmacological thromboprophylaxis (PTP) against VTE contribute to this high incidence, with time to initiation of PTP being the most readily modifiable risk factor. Besides the risk of VTE due to trauma, many patients present with higher VTE risk due to comorbidities (valve prosthesis, arrhythmias, hypercoagulable states).

The predicted risk for intracranial injury exacerbation has limited the use of early anticoagulation in the trauma patient with head injuries (2). Guidelines regarding the optimal time for VTE prophylaxis remain vague (3). Consequently, the initiation of PTP is based on individual case-by-case decisions or single-centre protocols that orientate on imaging findings, clinical examination or the physicians' experience (4). There is wide variability in practice regarding timing to start with PTP in patients with TBI. One of national surveys showed that 50% of respondents considered their practice on PTP in patients with TBI to be too conservative and 52% of included centers had no standardized protocols (5).

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Consequently, the main question remains: what is the balance between the incidence and complications of VTE in TBI patients on one side and risks of PTP on the other?

Venous thromboembolic risk in patients with traumatic brain injury

The association between injury and venous thromboembolic events is well recognized. The reported incidence of VTE after trauma varies from 6% to 58%. The incidence of VTE depends upon the patient characteristics, the nature of the injuries, the method of detection and the type of VTE prophylaxis (if any) used in the study population. Clinically significant PE has been reported in about 2% of major trauma patients with an associated mortality rate of 11% to 43% (6, 7).

Thirty-seven percent of pulmonary embolisms (PEs) in trauma patients occur in the first 4 days post-injury (8), and as many as 6% of PEs occur within 24 hours postinjury (9). Therefore, the patients would benefit from early thromboprophylaxis.

Traumatic brain injury has been identified as an independent risk factor for the development of VTE, which significantly deteriorates patient outcomes (10). Up to 58% of patients with isolated TBI without any thromboprophylaxis (mechanical or pharmacological) suffer from VTE (6). An association between the head injury severity and the risk of VTE has been shown: in patients with head/neck abbreviated injury scores (H/N AIS) of >2 the risk of VTE has been 2.5 times the risk compared to patients with H/N AIS ≤2 (11). Likewise, delaying the administration of PTP for more than 72 h has been shown to be an independent risk factor for VTE complications and mortality (12). Delaying VTE prophylaxis from 48 hours to 96 hours postinjury increases the risk of VTE by three times (13). Denson with colleagues showed a trend of increasing deep venous thrombosis (DVT) risk with increasing time to initiation of prophylaxis. The absolute risk of DVT increased from 3.6% in <24 hours group to 4.5% in 24 hours to <48 hours to 15.4% in >48 hours (14). Despite the use of mechanical and PTP a three- to fourfold increase in the DVT risk in patients with TBI was found (10).

Increased risk of DVT formation among patients with TBI can be explained by several causative mechanisms. Trauma induced coagulopathy has bimodal characteristics with initial hypocoagulopathy followed by a hypercoagulable state, leading to VTE and multiorgan failure (MOF) (15). Blood-brain barrier disruption and microvascular injury is followed by the release of procoagulant tissue factors from damaged brain parenchyma. Immobilization, activation of the extrinsic pathway, and elevated plasma levels of von Willebrand Factor are additional factors (16).

As duplex ultrasound screening and CT angiography are only performed in patients with high clinical suspicion of DVT and PE, the actual incidence of VTE may be underestimated. Consequently, clinically inapparent VTE events may be missed. Several studies identified patients that were at greatest risk for thromboembolic events and had the greatest potential to benefit from aggressive PTP. Factors associated with a higher risk of VTE included age, type of injury, length of stay, ventilator days, and other comorbidities. High-risk patients with TBI underwent weekly low-extremity venous duplex color-flow Doppler imaging (CFDI) surveillance (15) and the scan was positive for VTE in 25% of them. In comparison, VTE was diagnosed in 2% of all trauma patients and the incidence in trauma high-risk group was 18%. Among the patients with VTE and TBI 59% DVTs were diagnosed in the lower extremity above knee and 22% below knee. The rest of the patients (19%) had thrombosis in the subclavian vein. Femoral venous access was associated with significantly higher incidence of DVT, but with no PEs. An increased incidence of DVT was found in patients with intraparenchymal hemorrhage compared to patients with extra-axial hematomas. No associations between the incidence of VTE and AIS of the head or GCS on presentation were found. All patients received intermittent pneumatic compression device and 42% of patients received low-molecular weight heparin (LMWH) (15).

TBI patients diagnosed with VTE have a significantly longer ICU length-of-stay and an increased number of ventilator days (14). These data indicate the need for VTE surveillance in a population that is at great risk for VTE, especially those with intra-axial hematomas and potential long-term ICU stays.

Progression of intracranial hemorrhage in traumatic brain injury

The main concern associated with an early start of the prophylactic anticoagulation is a progression of the intracranial hemorrhage (ICH). It has been shown that there is a high likelihood of hematoma progression (expansion) already prior to the beginning of PTP: up to 45.9% of all TBI patients showed a spontaneous expansion of the hematoma (17). In another study, in patients with different types of intracranial hemorrhages, a spontaneous progression of hematoma was seen in 5 – 32% of patients, more in patients with intraparenchymal contusion or intraventricular hemorrhage (18). These high rates might be the consequence of frequent development of posttraumatic coagulation disorder in patients with isolated TBI, which significantly increases the risk of ongoing bleeding in the early phase after trauma (19). In addition, a subarachnoid hemorrhage has been found as a strong risk factor for spontaneous hematoma progression (in up to 56.5% of patients) (20).

After the initiation of VTE prophylaxis, the progression of hematoma was seen in up to 4 % of patients,

independently from the timing of VTE prophylaxis initiation. Craniotomies for emergent evacuation of acute ICH were performed in up to 8% of patients prior to the initiation of VTE prophylaxis. Following VTE prophylaxis, no patients required craniotomy in the early or late treatment groups (18).

Despite above stated data hematoma progression after initiation of PTP still remains a great concern. In a retrospective multicenter study, including more than 1200 patients with ICH, a hemorrhage progression was found in 14.5% of patients after initiating LMWH and 4.1% of those patients required neurosurgical intervention. Authors concluded that the safety of LMWH for VTE prophylaxis in patients with brain injury cannot be confirmed and the risk of using LMWH may exceed its benefit (21). On the contrary, other studies report that early VTE prophylaxis within the first 48 h after trauma is safe if the size of the hematoma in repeated head CT scans remains stable (22). Frisoli and colleagues reported radiographic expansion rates of ICH in 18% versus 17%, in the early (PTP within 24 h) versus the delayed cohort (48 h), consequently (23). In a study of Störmann and colleagues no significant differences in the rates of ICH expansion were found between the early, intermediate and late group. These numbers indicate that even an early initiation of VTE prophylaxis within the first 24 h of the clinical course in patients with severe TBI does not significantly increase the risk of bleeding progression compared to PTP started later. Risk factors associated with bleeding progression after the initiation of PTP included increasing age, male sex, head AIS and subarachnoid bleeding. Therefore, these patients need to be carefully clinically and radiologically monitored for signs of hematoma progression. Nevertheless, the time of PTP initiation was not proven to be a risk factor for intracranial bleeding progression in the context of the studies (17).

Venous thromboembolic prophylaxis after traumatic brain injury

Prophylaxis against thromboembolic complications is of utmost importance in all trauma patients and it has been shown to reduce the rate of VTE, in particular if started within the first 72 h after the injury (24). The first measures for prevention of VTE include mechanical methods (graduated compression stockings and intermittent pneumatic compression devices). The data on their efficacy are less compelling, although they are attractive because of the low rate of associated complications. An incidence of VTE in patients with isolated TBI has been reduced with the use of above-mentioned devices, however the data is scarce (14). In a small study the efficacy of pneumatic leg compression has been shown only in patients with TBI (7).

The effectiveness of mechanical thromboprophylaxis methods is significantly increased with the addition of PTP. It was shown that the VTE rate in patients with severe head trauma who were treated also with PTP was reduced below 10% (25), with the use of enoxaparin the rate of PE was 0% (26).

Optimal timing of PTP initiation has been controversially discussed in the literature. In 2018, Hachem (25) noticed that PTP in severe TBI is often delayed by more than three days after injury. Numerous clinical studies have demonstrated that an early beginning of pharmacotherapy significantly reduces the rate of VTE in TBI patients by approximately 50% (27). Byrne et al. conducted a retrospective cohort study in patients with severe TBI (22). Administration of VTE prophylaxis within 72 h of trauma was associated with lower rates of both pulmonary embolism (OR, 0.48; 95% CI, 0.25–0.91) and deep vein thrombosis (OR 0.51; 95% CI, 0.36–0.72), but there was no increase in risk of late neurosurgical intervention or death when compared with late prophylaxis (after 72 h). Retrospective studies showed that late prophylaxis (>72 h) is associated with higher VTE rate in patients with moderate-to-severe TBI, higher rate of tracheostomy, longer duration of mechanical ventilation and stay in the hospital, lower discharge Glasgow coma scale; however, there was no difference in survival between early (>72 h) and late group (28).

Margolick with colleagues in their systematic review recommend that administering PTP after 24 h following injury may be safe in low-risk TBI patients and stable radiographic findings (29). Störmann (17) found out, that even in patients with severe TBI, the administration of LMWH within 24 h did not increase the frequency of bleeding progression compared to the later initiation of PTP. Besides this, administration of PTP during the first 24 h after trauma significantly reduces the rate of VTE events in TBI patients (30). Despite combined mechanical and PTP, the rate of thromboembolic events in TBI patients remained high (31) if the PTP was administered > 24h. For these reasons, early start of PTP after trauma seems to be of utmost importance.

Most of the authors studied only patients with low hemorrhage risk according to the modified Berne-Norwood criteria (26): patients with stable hemorrhagic lesions (no increase in size or number of lesions between admission and follow-up CT scan at 24h). Also, Rivas with colleagues found that early PTP is not associated with progression of ICH or need for neurosurgical intervention in patients with blunt TBI, however the authors emphasized the importance of a stable follow-up head CT, which was performed 6 hours following injury (32). Another emphasis has been put on the discussion about the initiation of PTP with the neurosurgical consultant (12).

Patients who undergo urgent neurosurgical interventions for TBI are typically considered to be at a high risk of developing VTE. Byrne with colleagues showed in a multicentric study on 4951 patients that

early PTP was associated with reduced risk of thromboembolism. However, earlier initiation of prophylaxis was associated with increased risk of repeated neurosurgery. During the first 3 days, each additional day of prophylaxis delay was associated with a 28% decrease in odds of repeated neurosurgery (OR, 0.72 per day). After 3 days, each additional day of prophylaxis delay was associated with an additional 15% decrease in odds of repeated neurosurgery (OR, 0.85 per day). Authors advised a caution with the initiation of PTP particularly during the first 3 days after the initial surgical intervention (33).

In patients with hemorrhage progression on initial follow-up head CT PTP itself is associated with a 13-fold increased odds of further hemorrhage progression, which can be clinically significant (need for craniotomy/craniectomy or drop in GCS ≥2). The timing of prophylaxis (before or after 72h) was not found to be associated with subsequent hematoma progression (34). Nonetheless, this high-risk group is the most challenging to manage. Because many such patients are excluded from studies, there are very few data upon which to base a strategy. Authors of ACS TQIP best practices in the management of TBI suggest the use of retrievable inferior vena cava (IVC) filter or the routine surveillance of the lower extremity with duplex ultrasound (35).

Patients with TBI requiring VTE prophylaxis are often compared with patients undergoing elective neurosurgical procedures as they also receive PTP in the form of LMWH to prevent VTE complications. In one of the studies one group of patients received enoxaparin (within 24 hours postoperatively) and pneumatic compression device as VTE prophylaxis and the other group only pneumatic compression device. No significant difference in the postoperative incidence of ICH was found between the groups (36). The same results were found with nadroparin (37). These results suggest the ICH progression following VTE prophylaxis may be attributable to natural progression alone.

In the absence of large-scale randomized trials the choice of antithrombotic agent is largely based on physician's and institutional preference. In majority of trials LMWH (enoxaparin) and unfractionated heparin (UFH) were used. In a study by Benjamin with colleagues (12), the authors were able to demonstrate that PTP with LMWH is superior to UFH with regards to survival and prophylactic benefit. Another study showed a significantly lower rate of pulmonary embolism with LMWH compared to UFH (1.4% vs 2.4%; OR, 0.56) (38). In addition, LMWH has been associated with lower rates of heparin-induced thrombocytopenia and traumatic hematoma expansion (39). Geerts with colleagues demonstrated that patients receiving enoxaparin had a 6% rate of proximal DVT documented by venography, compared with a 15% rate in injured patients receiving low dose, unfractionated heparin as prophylaxis (40). On the other hand, UFH has a shorter half-life and is more easily reversed. Therefore, UFH may be the preferred agent in high-risk situations with expanding hemorrhagic TBI lesions. In a study by Dudley and colleagues no significant difference between enoxaparin and dalteparin was found in terms of hematoma progression or the rate of VTE (24).

What is the benefit of adjustment of LMWH dosage by anti-Xa factor trough level in plasma? A plasma trough level of >0.1 IU/mL is considered as an adequate prophylactic level. In a study on trauma patients receiving a standard prophylactic enoxaparine doses (30 mg/12h) sub-prophylactic anti-Xa troughs were noted in 83.9% of patients. To reach plasma trough levels > 0.1 IU/mL an increase in enoxaparine dose to 40 mg twice daily was necessary. In the higher dose group a significantly lower VTE rate was found with no difference in hemoglobin level (41).

Vena cava filters have been placed in patients with acute proximal DVT or a recent PE who have either a contraindication to receiving anticoagulating doses of heparin, who have developed a bleeding complication while on heparin, or who have had a PE despite adequate anticoagulation (42). Routine use of IVC filters is not recommended. First, IVC filters do not prevent DVT, and, in fact encourage the development of DVT and may result in caval thrombosis and the long-term postphlebitic syndrome. Other complications with filters include migration, tilt, caval perforation and PE (43). Besides, also PE rate in injured patients is small (up to 0.13% and 0.21% in patients with risk factors) (44). Vena cava filter could be considered in a few selected patients who are considered to be at extremely high risk for VTE, who have the need for repeated surgical procedures, and who have contraindications to anticoagulation, even at prophylactic doses. They should be removed immediately when patients can safely receive PTP.

Anticoagulation therapy in patients with traumatic brain injury

The optimal initiation of therapeutic anticoagulation (TAC) or antiplatelet therapy following TBI is unclear. There is very scarce data on the resumption of therapeutic doses of antithrombotics after hemorrhagic TBI.

In one of the studies patients in the early TAC group (within seven days of injury) with UFH infusion demonstrated no clinically significant evidence of progression of ICH and none required additional neurosurgical intervention (45). Byrnes with colleagues started with TAC at least 7 days after injury (mean time to initiation of 11.9 days) and 96% of patients had stable ICH (46). On the other hand, patients with 'clinical deterioration' following TAC were associated with significantly earlier initiation of TAC (4.5 days), com-

pared to 11 days in the 'no deterioration' group (47). These findings support the initiation of TAC several days postinjury, in concurrence with vigilant monitoring of neurologic status and repeated head CT scans. In a review of literature Tykocki with colleagues found that resuming antithrombotic therapy early (3–17.5 days) after TBI may carry an acceptably low risk of hemorrhagic complications, and that the risk of complications may be lower with novel oral anticoagulants (NOACs) than with vitamin K antagonists (48). In patients with atrial fibrillation and intracerebral hemorrhage the benefits of anticoagulation therapy (reduced risk of vascular death and nonfatal stroke in high-risk patients) seemed to be greatest when it was resumed 7–8 weeks after intracerebral hemorrhage, and there was no significant increase in the risk of severe hemorrhage. Risk prediction tools (CHA2DS2-VASc and HASBLED) have not been validated for TBI patients with preinjury anticoagulation therapy. In agreement with international guidelines for the management of spontaneous intracerebral hemorrhage (49), therapeutic anticoagulation may be continued after 10–14 days after TBI in patients with a stable injury and a high risk of cerebral ischemia (mechanical valve prosthesis or non-valvular atrial fibrillation and a CHA2DS2VASc score ≥ 4). In patients with moderate or low risk of thromboembolic events, it may be more appropriate to resume anticoagulation after 4–8 weeks.

There is little evidence to guide the resumption of TAC for patients who have a mechanical heart valve and concurrent TBI. Kuramatsu et al. demonstrated that the hazard ratio for restarting TAC prior to day six increased the risk for hemorrhagic complications, whereas restarting beyond day 13 resulted in less hemorrhagic complications; however, additional delay increased the risk for VTE (47).

In conclusion, patients who are 7–12 days postinjury should be considered for TAC initiation, after considering the risks and benefits of both hemorrhagic and thromboembolic complications on an individual basis. Expertise from a multidisciplinary team with experience of clinical practice should be sought. Patients with the greatest need for anticoagulation (mechanical heart valve) or antiphospholipid syndrome with recurrent thromboembolic events require earlier resumption of anticoagulation. In selected cases, heparin-bridging therapy may be considered (50).

Guidelines

The quality of the evidence for the development of guidelines for thromboembolic prophylaxis in patients with TBI is low. The majority of the studies are retrospective, with low number of patients, besides this the incidence of VTE was determined according to clinical signs and symptoms with very few studies using routine ultrasound surveillance. Given the limitations of retrospective studies and the reliance on clinical signs and symptoms, it would be beneficial to have prospective studies with larger sample sizes and routine ultrasound surveillance to provide more robust evidence regarding the incidence of VTE and the effectiveness of thromboprophylaxis in patients after urgent neurosurgical interventions for TBI.

Brain Trauma Foundation is revising and publishing guidelines for the management of severe TBI. In their latest update in 2016 (3) they acknowledged limited evidence base for making recommendations. There was insufficient evidence to support a Level I or II recommendation for DVT prophylaxis in severe TBI patients. Level III recommendations were:

- Low molecular weight heparin or low-dose UFH may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.
- In addition to compression stockings, PTP may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of PTP for deep vein thrombosis.

A consensus of Austrian expert group in 2019 addressed the optimal timing and preferred agent for PTP in patients after hemorrhagic TBI. Firstly, authors recommended initiating thromboembolism prophylaxis 24 h after injury in patients who have a clinically and radiographically stable TBI. In addition, they recommended LMWH as the agent of choice, at a dose suitable for patients with a high risk of thrombosis (e.g., subcutaneous enoxaparin 4000 IU once daily). Secondly, should therapeutic anticoagulation be resumed after hemorrhagic TBI and when? There is insufficient evidence to support or discourage the resumption of therapeutic antithrombotic treatment following TBI and also for timing (51). Expertise from a multidisciplinary team with experience of clinical practice should be sought to guide decision making on a case-by-case basis.

A more recent clinical consensus document of the American Association for the Surgery of Trauma Critical Care Committee recommended the initiation of PTP as soon as possible following TBI (24–72 hours following admission), pending stability of intracranial/extra cranial hemorrhage and in conjunction with neurosurgical consultation (52).

In 2015, the American College of Surgeons Trauma Quality Improvement Project (TQIP) released guidelines on TBI management supporting consideration of VTE prophylaxis within the first 72 hours of hospitalization, following a stable head CT (35). To provide some objective assessment of the risk of progression and to guide the timing of initiation of prophylaxis,

Table 1. Modified Berne-Norwood criteria

Low risk	Moderate risk	High risk
No moderate or high risk criteria	Subdural or epidural hematoma >8 mm Contusion or intraventricular hemorrhage >2 cm Multiple contusions per lobe Subarachnoid hemorrhage with abnormal CT angiogram Evidence of hematoma progression at 24 hrs	ICP monitor placement Craniotomy Evidence of progression at 72 hrs
Initiate pharmacologic prophylaxis if CT stable at 24 hrs	Initiate pharmacologic prophylaxis if CT stable at 72 hrs	Consider placement of an inferior vena cava filter

Berne and others derived the Modified Berne-Norwood criteria (Table 1) (53). Timing of prophylaxis initiation in TBI should be individualized and based on individual patient characteristics, the overall clinical context, and expert judgment.

Conclusions

Traumatic brain injury carries very high risk of venous thromboembolism, therefore thromboembolic prophylaxis should be initiated as soon as possible. Mechanical prophylactic devices should be used immediately, whereas pharmacologic thromboprophylaxis should be considered after follow-up head CT scan without hematoma progression (within 24–48 hours). The decision should be based on careful consideration of the risks of hemorrhagic progression and thromboembolic complications on an individual patient to patient basis.

There is a clear need for further randomized controlled trials to determine the optimal timing, agent, and dose for PTP in TBI. Probably, time to stabilization of hemorrhage could be the time frame for the safe initiation of PTP.

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