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Analysis of Factors Associated to Hemorrhagic Transformation After Recanalization of Acute Ischemic Stroke

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Abstract: Ischemic stroke is associated with high rates of mortality and disability, making it an urgent issue that requires immediate attention. However, patients with acute ischemic stroke (AIS) can open the occluded cerebral vessels timelier, restore cerebral perfusion, save the ischemic penumbra, and bring better prognosis. However, a considerable number of patients still have poor clinical outcome due to complications such as hemorrhagic transformation (HT) after vascular reopening. The specific mechanism of HT after recanalization treatment is currently not fully understood. Studies have shown that multiple factors are associated with bleeding transformation after mechanical thrombectomy in AIS patients. Some studies suggest that the damage of ischemia and reperfusion and vascular permeability may play a role. This paper summarizes the possible mechanisms and related influencing factors of HT after vascular recanalization treatment of AIS patients to further guide the treatment and management decisions of AIS patients.

Keywords: Acute Ischemic Stroke; Vascular Recanalization Therapy; Hemorrhagic Transformation; Endovascular Therapy; Bridging Therapy; Risk Factors.

1. Hemorrhagic Transformation in Acute Ischemic Stroke

Results from the reperfusion of blood vessels in the ischemic region following an acute cerebral infarction. This includes hemorrhage that occurs naturally (spontaneous hemorrhagic transformation) as well as hemorrhage (secondary/therapeutic hemorrhagic transformation) that arises subsequent to intervention measures (including thrombolysis, thrombectomy, and anticoagulation) [5]. The site of hemorrhage can be within the infarcted area or at a distant location from the infarct. The definition most commonly used in current research is as follows: intracranial hemorrhage is identified on a subsequent head CT/MRI, which was not detected on the initial post-cerebral infarction CT/MRI examination, or hemorrhagic infarction can be confirmed based on the findings of the first head CT/MRI.[1-4] [6]

Based on the presence or absence of neurological deficit aggravation, it can be classified into symptomatic intracranial hemorrhage (sICH) and asymptomatic intracranial hemorrhage. Western countries have shown greater concern for symptomatic intracranial hemorrhage, with fewer studies on asymptomatic intracranial hemorrhage. However, recent research suggests that some asymptomatic intracranial hemorrhage can also lead to adverse prognosis, particularly in terms of long-term cognitive and neurological impairment, which may potentially convert to symptomatic intracranial hemorrhag[7].The National Institute of Neurological Disorders and Stroke confirmed that the incidence of hemorrhagic transformation after the combination of rt-PA thrombolysis and mechanical intra-arterial thrombectomy is 10.5%, with most hemorrhages occurring within 36 hours after bridging therapy[8],The European Cooperative Acute Stroke Study found that the incidence of symptomatic intracranial hemorrhage after bridging therapy is 4.5%[9].At present, there is a paucity of large-scale clinical epidemiological data on hemorrhagic transformation in the Chinese population, warranting further investigation.

2. The Mechanism of Hemorrhagic Transformation

Regarding the mechanism of hemorrhagic transformation, it is currently believed that post-revascularization treatment-related hemorrhagic transformation may be associated with vascular endothelial damage, vascular wall injury following the disruption of the blood-brain barrier, reperfusion injury, the use of thrombolytic agents, as well as the combined use of antiplatelet and anticoagulant therapies[6].Additionally, some scholars have proposed that the mechanisms of early and late hemorrhagic transformation may differ based on the timing of their occurrence, and this remains to be further investigated and elucidated.

3. Risk Factors for Hemorrhagic Transformation

Although ischemic stroke itself and ischemia-reperfusion injury following vascular recanalization play a major role in hemorrhagic transformation after infarction, the probability of hemorrhagic transformation varies among patients due to differences in their medical history, age, gender, and the nature of the infarction. Identifying the risk factors associated with hemorrhagic transformation can play a significant role in the prevention of hemorrhage and in potential treatment decisions.

3.1. Blood Glucose

In patients with acute ischemic stroke (AIS), hyperglycemia at admission is known to affect patient prognosis[10].Studies have shown that in AIS patients receiving intravenous thrombolysis with alteplase, hyperglycemia at admission is associated with an increased risk of death, symptomatic intracranial hemorrhage, and severe neurological deficits[11].Other studies have also confirmed that hyperglycemia on admission leads to a worse clinical outcome in AIS patients with mechanical thrombectomy[12-15].Recent studies have found that post-procedure hyperglycemia in AIS patients who have undergone mechanical thrombectomy increases the risk of symptomatic intracranial hemorrhage and parenchymal hematoma. Persistent hyperglycemia (>140 mg/dL), particularly in patients with elevated blood glucose levels persisting for 24 hours post-mechanical thrombectomy, significantly increases the risk of hemorrhagic transformation [16].

3.2. Hemodynamics

In patients with acute ischemic stroke, the sustained elevation of systolic blood pressure and the disruption of cerebral autoregulation are associated with hemorrhagic transformation. Currently, there are no domestic guidelines that explicitly state the blood pressure control range for patients undergoing mechanical thrombectomy before and after the procedure. International guidelines suggest that patients undergoing mechanical thrombectomy should maintain a blood pressure of below 180/105 mmHg[17] to promote perfusion of the ischemic area while reducing the risk of potential intracranial hemorrhage. Recent studies suggest that within the first 24 hours after mechanical thrombectomy, patients with higher peak systolic blood pressure or greater hemodynamic variability have a higher probability of hemorrhagic transformation[18].Although higher blood pressure may be beneficial for patients with incomplete vascular recanalization by promoting perfusion of the ischemic penumbra, it may also lead to relative overperfusion. Studies have found that when blood pressure fluctuations exceed an individual's autoregulatory threshold, the risk of hemorrhagic transformation increases[19].

In patients with successful vascular recanalization, the rate of hyperperfusion is relatively high after mechanical thrombectomy. Studies have already demonstrated that post-reperfusion hyperperfusion can impact hemorrhagic transformation and prognosis[20,21].The detection of hyperperfusion rates can be achieved by assessing blood flow in the middle cerebral artery territory using arterial spin labeling MRI, which can guide the prevention of hemorrhagic transformation[20].Therefore, blood pressure control-centered perioperative management is an important measure for preventing hyperperfusion syndrome.

3.3. Stroke Subtype

Stroke subtype is an independent risk factor for hemorrhagic transformation within 24 hours after endovascular treatment in patients with acute large vessel occlusion. A large-sample, multicenter retrospective study confirmed that compared to patients with large artery atherosclerotic stroke, those with cardioembolic stroke had a higher incidence of parenchymal hematoma, symptomatic intracerebral hemorrhage, and any intracranial hemorrhage[22].Furthermore, after mediation analysis, it was found that the more times a thrombectomy was performed in cardioembolic stroke patients, the more significant the promotion of the association between stroke subtype and the increased risk of hemorrhagic transformation[22].In cardioembolic stroke, the embolus rapidly enters the intracranial circulation from the heart via the bloodstream, which is more abrupt and lacks the collateral circulation and ischemic preconditioning resulting from long-term vascular stenosis, potentially leading to a larger volume of core infarction and a lower degree of mismatch between the infarct core and the ischemic penumbra, further exacerbating the risk of hemorrhagic transformation[23].The difference in thrombus composition during large vessel occlusion may result in varying difficulty in thrombectomy, with studies showing that fibrin-rich thrombi are more difficult to remove and require more thrombectomy attempts compared to red cell-rich thrombi[24-26].Cardioembolic thrombi often form over a longer period and are mainly composed of fibrin and platelet aggregates, making their structure denser compared to the atherosclerotic thrombi composed of red cell clumps, and therefore more difficult to excise[27-29].Repeated thrombectomy attempts may lead to vascular injury and blood-brain barrier disruption, increasing the risk of hemorrhagic transformation.

3.4. Baseline NIHSS Score

The National Institute of Health Stroke Scale (NIHSS) score primarily reflects the degree of neurological deficit. A higher NIHSS score at the time of onset implies a larger infarct size or poorer collateral circulation. In a retrospective study that included 633 patients with anterior circulation AIS undergoing mechanical thrombectomy alone or in combination with intravenous thrombolysis, multivariate analysis confirmed that a higher baseline NIHSS score was an independent risk factor for the occurrence of sICH after acute thrombectomy[30].In another study that included 127 patients with anterior circulation AIS receiving mechanical thrombectomy, multivariate analysis similarly found that the NIHSS score was associated with the occurrence of sICH following mechanical thrombectomy in AIS patients[31].This may be due to the NIHSS score reflecting the severity of neurological deficits and the size of the infarct volume, which is positively correlated with the incidence of HT[32].

3.5. Alberta Early CT Score of Stroke Items

The Alberta Stroke Program Early CT Score (ASPECTS) is used to evaluate the extent and distribution of acute ischemic changes in brain tissue. The score reflects the severity of the stroke, with a lower score indicating a larger core infarct volume and a more severe stroke, resulting in greater damage to brain tissue and the blood-brain barrier (BBB), and the higher the BBB permeability. Recent studies have found that a lower ASPECTS score increases the risk of intracranial hemorrhage after thrombectomy, with a significant increase in risk when the score is ≤7 points [33,34]. The assessment of infarct volume through ASPECTS further confirms the correlation between infarct volume and the occurrence of hemorrhage after thrombectomy. The larger the volume of cerebral infarction, the higher the risk of postoperative hemorrhage, highlighting the importance of assessing the patient's infarct volume before thrombectomy.

3.6. The Vascular Recanalization Time

Preoperative cranial CT scans have revealed low-density shadows, indicating a longer duration of brain tissue ischemia and vascular occlusion. A study by Alvarez-Sabin and colleagues have demonstrated that the presence of low-density foci in the brain parenchyma on preoperative cranial CT scans is a predictive factor for hemorrhagic transformation (HT), with a positive predictive value of up to 77% and a negative predictive value as high as 94%[35]. Kass-Hout and colleagues analyzed the impact of the time from femoral artery puncture to vascular recanalization on clinical outcomes in acute ischemic stroke (AIS) patients and found that the longer the time to recanalization, the higher the incidence of postoperative hemorrhagic complications. When the time from AIS onset to femoral artery puncture exceeds 270 minutes, the risk of hemorrhage[33]. These studies indicate that the time to recanalization is positively correlated with the occurrence of HT in AIS patients. The reason may be that as the time for vessel recanalization extends, the area of brain tissue infarction increases, vascular wall permeability rises, the risk of reperfusion injury grows, and the incidence of HT increases. Additionally, a longer time to recanalization suggests more complex lesions and a higher thrombus burden, leading to an increased number of thrombectomy attempts and more severe vascular endothelial injury[36].Studies have found that more than three thrombectomy attempts is an independent predictive factor for postoperative hemorrhage [37],Therefore, reducing the number of thrombectomy attempts, shortening the time to recanalization, and decreasing the risk of post-thrombectomy hemorrhage can become future research directions for endovascular treatments.

3.7. Collateral Circulation

Collateral circulation refers to the blood flow that reaches the ischemic area through collateral vessels or new vascular anastomoses when there is severe stenosis or occlusion of cerebral blood vessels. Studies have found that a collateral grade of less than 2 according to the American Society of Interventional and Therapeutic Neuroradiology (ASITN)/ Society of Interventional Radiology (SIR) collateral grading system can increase the risk of hemorrhage after thrombectomy[33].Research by Wufuer et al. has shown that good collateral circulation can reduce the risk of HT in AIS patients[38].Collateral circulation helps maintain blood supply to the ischemic penumbra, prevents further expansion of the infarct core, reduces the destruction of the BBB, and decreases the release of inflammatory factors from brain tissue infarction, while also maintaining the structural and functional integrity of the vascular endothelium. Additionally, collateral circulation can predict the size and severity of the infarct area in AIS patients. Therefore, poor collateral circulation during acute cerebral infarction can result in a smaller ischemic penumbra, a larger infarct core volume, and an increased risk of postoperative hemorrhage. Consequently, preoperative assessment of collateral circulation using cranial MRA or cervical CTA and DSA can help further clarify the risk of post-thrombectomy hemorrhage.

3.8. Other Related Risk Factors

The neutrophil-to-lymphocyte ratio (NLR), reduced platelet count, and advanced age are associated with hemorrhagic transformation after mechanical thrombectomy for large vessel occlusion. An imbalance in the neutrophil-to-lymphocyte ratio is the basis of the inflammatory response and can more objectively reflect the body's inflammatory state; a higher value indicates a stronger inflammatory response. Previous studies have identified that an NLR greater than 0.83 is associated with symptomatic intracranial hemorrhage in AIS patients after thrombectomy[33].Similarly, a reduced platelet count and age over 80 are independent risk factors for HT after vascular recanalization therapy[18].

4. Prospection

AIS is a significant health condition that profoundly impacts patient outcomes. Vascular recanalization therapy, a critical treatment modality, is associated with the risk of HT. Prompt diagnosis of AIS and early identification of HT are essential for effective hemorrhage monitoring and the adjustment of subsequent treatment protocols. Advancements in interventional techniques and equipment are likely to facilitate the broader adoption of bridging therapy in clinical practice. Looking ahead, it may become feasible to more accurately identify hemorrhage risk factors and reduce the incidence of HT.

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