

Review

The Pathophysiological Mechanism and Treatment of Secondary Brain Insult of Hypertensive Intracerebral Hemorrhage

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Keywords

Hypertensive intracerebral hemorrhage · Secondary brain insult · Pathophysiological mechanism · Integrative treatment

Abstract

Hypertensive intracerebral hemorrhage (HICH) is a type of acute cerebrovascular disease with high rates of incidence, mortality, and disability, and is a cause of more frequent instances of secondary brain insult (SBI). In-depth study of the pathogenesis and pathophysiological mechanisms of SBI in HICH contributes to its clinical treatment and prognosis. This article presents a brief summary of the pathophysiological mechanism and treatment of SBI after HICH.

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Introduction

Secondary brain insult (SBI) is a secondary cerebral injury following a primary brain insult. It can aggravate a primary brain insult and brain edema, prolonging pathological progression of the disease [1, 2]. It is referred to as SBI after a hypertensive intracerebral hemorrhage (HICH) that occurred in the progress of treatment or after natural progression of the disease, which is an important factor for exacerbation and acute death. However, an effective means for the prevention and treatment of SBI, which includes Western medicine, traditional medicine, as well as complementary and alternative medicine, has not been

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discussed in detail, so in-depth study of the pathogenesis and pathophysiological mechanisms is necessary. The diagnostic criteria of SBI, the pathophysiological mechanism, and the potential treatments of SBI after HICH were reviewed as follows.

Definition of SBI

According to reliable research [3–5], we suggest the following diagnostic criteria for SBI: In the 2 weeks since the disease occurred and the symptoms are stable, if the patient has (1) temperature $\geq 39.0^{\circ}\text{C}$ for >4 h, (2) blood pressure $\leq 90/60$ mm Hg for >2 h or systolic blood pressure <90 mm Hg, (3) $\text{PaO}_2 \leq 60$ mm Hg, (4) fasting blood glucose ≥ 9 mmol/L, (5) electrolyte disorder or acid-base imbalance, and (6) intracranial pressure (ICP) >2.9 kPa or cerebral perfusion pressure (CPP) <9.3 kPa. If three or more of the above are present, the possibility of SBI should be considered.

Potential Pathophysiological Mechanism of SBI after HICH

Fever

The edema or hematoma after HICH compresses the heat dissipation center in the thalamus, causing ischemia or secondary bleeding. The result is that the thalamus loses its central heat dissipation function and fever develops. The fever aggravates brain injury [6]. Secondly, tissue necrosis, absorption after erythrocyte rupture, and secondary infection are also related to the fever that develops. Thirdly, brainstem hemorrhage blocks the pathway for thermoregulation by the thalamus and reticular structure, which is also an important factor. Hyperthermia can increase oxygen consumption and accelerate energy metabolism, which can promote the production, uptake, and release of endogenous harmful factors and aggravate cellular acidosis, and then lead to cell edema and SBI. Globus et al. [6] found that higher temperatures were associated with an increase in oxygen free radical production, which caused neuronal death. In addition, animal experiments have demonstrated that, after ischemia, changes in ATP, phosphocreatine, and calcium/calcium-dependent protein kinase II levels are all temperature dependent; hypothermia can decrease the brain metabolism rate and then decrease lactic acid accumulation mediated by ischemia, while hyperthermia aggravates lactic acid accumulation and accelerates neuronal death [7].

Hypotension

Liu et al. [8] proposed that hypotension in early HICH is mainly caused by impaired brainstem function and effective circulation hypovolemia due to massive bleeding, frequent dehydration, as well as eating and fluid infusion deficiency. Hypotension directly causes decreases in cerebral blood flow (CBF) and CPP, which in turn result in hypoxic ischemia. As the final result, ATP scarcity and membrane pump function failure lead to cell edema and even death. In addition, it is worth mentioning that the brain edema after ischemia due to hypotension mainly affects peripheral artery areas, while the brain edema caused by simple hypoxemia affects the whole brain. Zhou et al. [9] found that the content of TXA2 was increased by creating a rat model of diffuse brain injury and SBI including hypotension, and stated that hypotension might cause brain vasospasm and microthrombus formation, which decrease CBF and aggravate primary cerebral injury.

Hypoxemia

Liu et al. [8] proposed that the pathomechanisms of hypoxemia are different during different periods of disease. At the early stage, the sympathetic nervous system is overexcited, and the increased norepinephrine and epinephrine levels in the blood play an important role in hemodynamics and pulmonary pathophysiological changes. At the late stage, the airway secretions of a coma patient increase and phlegm expulsion decreases, and when combined with infection, all of these can damage pulmonary ventilation and gas exchange. All of the above in the end cause hypoxemia.

As is well known, the pneumotaxic center is located in the upper region of the pontine, while the apneustic center is at the bottom, the respiratory center is located in the medulla, and the advanced nerve center of the autonomic nerve is located in the thalamus. After HICH, ICP increases, CBF becomes deficient, and oxygen is insufficient, so neuronal synaptic transmission and cerebrovascular regulation are impaired or even lost, which results in abnormal respiration. Brain tissue is very sensitive to anoxia. The brain weighs only about 2% of the total body weight, while CBF accounts for 15% of cardiac output, and the oxygen consumed by the brain accounts for 23% of total oxygen uptake. However, the cerebral oxygen reserve is so low that it is completely consumed after the cerebral circulation has ceased for 10 s. Moreover, when brain tissue is in a hypoxic state, metabolic acidosis will occur, which can increase cerebrovascular permeability, aggravate brain edema, and increase intracranial hypertension. Furthermore, hypoxemia can give rise to hyperventilation by exciting aortic and carotid receptors. Hyperventilation increases the $\text{HCO}_3^-/\text{H}_2\text{CO}_3$ ratio, resulting in alkalemia, which prevents oxygen release from HbO_2 , and thus the brain tissue becomes more oxygen deficient [10].

Hyperglycemia

It is generally accepted that stress leads to hyperglycemia after HICH. Zhang and Huang [11] believed that stress hyperglycemia is mainly caused by the following reasons: (1) The space-occupying effect of HICH hematoma and tissue edema stimulates the hypothalamic-pituitary-target gland axis, which causes sympathetic-adrenal system hyperfunction and then promotes the secretion of blood sugar hormones, such as cortisol, growth hormone, glucagon, and catecholamines, which leads to hyperglycemia. (2) Mannitol, antihypertensive drugs, and hormones inhibit the secretion of insulin and its sensitivity. (3) A decline in serum insulin concentration or the development of insulin resistance in peripheral tissues all reduce glucose metabolic utilization, which then elevates blood sugar levels. (4) After HICH, the brain stem sugar-regulating center is impaired and sugar adjustment becomes imbalanced, leading to hyperglycemia. Hyperglycemia increases lactic acid, directly injures brain tissue, and increases the production of CO_2 . High concentrations of CO_2 can directly dilate blood vessels and increase CBF and ICP, eventually leading to brain damage [12, 13]. In addition, Zhang and Huang [11] studied the effects of dynamic changes in serum tumor necrosis factor alpha and interleukin 6. Their results suggest that after a rise in blood glucose due to HICH, tumor necrosis factor alpha and interleukin 6 levels are high. Therefore, we can deduce that high blood glucose can promote cell apoptosis by inducing inflammation. Moreover, high blood glucose levels also aggravate cerebral edema by promoting free radical generation and inducing bradykinin.

Electrolyte Disorder

Electrolyte disorder manifests as high sodium, high chloride, low sodium, low chloride, low potassium, and high potassium. Hypernatremia, hyperchloremia, and hypokalemia account for 1/4, respectively, and hyponatremia and hypochloremia account for 1/4, respectively. Hypernatremia, hyponatremia, and hypokalemia are the most common, and

the details are as follows. Hyponatremia is closely related to the bleeding site for the following reasons: (1) Encephalorrhagia ruptured to ventricle thalamus hemorrhage (cerebral hemorrhage ruptures into the ventricle or thalamus hemorrhage) causes hypothalamus damage and reduces the secretion of antidiuretic hormone, which leads to central diabetes insipidus [14]. (2) Cerebral hemorrhage stimulates the subcutaneous higher center of the sympathetic nerve, excites sympathetic nerves, and increases sodium reabsorption. (3) The hypothalamus pituitary system injury results in abnormal adrenocorticotropic hormone levels and then promotes the secretion of aldosterone and sodium. (4) The hypothalamus injury causes autonomic nerve dysfunction, which results in increases in sweating, moisture loss, and serum sodium. Hyponatremia is often caused by secondary causes, such as long-term use of high-ceiling diuretics like furosemide or thiazide, or because the patient cannot eat and the amount of fluid supplement is low or the brain injury causes inappropriate antidiuretic hormone secretion. The main reasons for the development of hypokalemia are: (1) Lack of potassium intake; HICH patients usually cannot eat and experience potassium deficiency. (2) The inappropriate use of diuretics: on the one hand, diuretics strengthen sodium potassium exchange, causing loss of potassium through the inhibition of sodium chloride ion reabsorption. On the other hand, low blood volume stimulates aldosterone secretion, which eliminates potassium and then leads to low potassium. (3) Vomiting causes metabolic alkalosis, and then renal tubule H^+Na^+ exchange is reduced, which leads to K^+Na^+ exchange strengthening, ultimately causing the elimination of potassium. Moreover, metabolic alkalosis can lead to hypokalemia by transferring potassium from the cell exterior to interior. (4) Insulin transfers extracellular potassium into the cell. Electrolyte imbalance can cause damage to brain cell membranes, which reduces ATPase activity and induces phospholipid metabolic disorders. An abnormal distribution of internal and external membrane sodium, potassium, calcium, and magnesium ions can damage the blood-brain barrier, resulting in the net outflow of plasma proteins or electrolytes through the vessel wall, increased extracellular osmotic pressure and water sodium retention, and aggravation of cerebral edema.

Acid-Base Imbalance

Chen [15] stated that metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis are the most common types of acid-base imbalance after HICH. The causes of respiratory acidosis include (1) hematoma, edema and cerebral hernia in a cerebral hemorrhage that depress the apneustic center, (2) bursting out acute respiratory distress syndrome, and (3) a history of chronic obstructive pulmonary disease. The causes of respiratory alkalosis include (1) intracranial hypertension after HICH has excited the respiratory center, which leads to hyperventilation, (2) hypoxia due to a variety of reasons, (3) tachypnea caused by hyperpyrexia, infection, pain, or other factors, (4) anxiety, hyperventilation, etc., and (5) nonstandard artificial assisted respiration. The causes of metabolic acidosis include (1) lactate accumulation caused by high energy consumption during a state of stress, hypoxemia, secondary epilepsy, secondary infection, ardent fever, shock, and others, (2) ketoacidosis, (3) diuretics, ischemia, and hypoxia causing renal function damage, which reduces the elimination of acidic substances, and (4) high-energy nutrient fluids such as cationic acid and solutions without HCO_3^- , which all can cause hyperchloremic metabolic acidosis. The causes of metabolic alkalosis include (1) long-term use of diuretics or glucocorticoids, (2) potassium deficiency, and (3) alkaline drug abuse and alkalosis after hypercapnia. When acid-base imbalance occurs, glutamate decarboxylase activity is enhanced and gamma-aminobutyric acid production is increased, the latter causing general depression of central neurons. In addition, acid-base imbalance adversely affects phosphorylation and decreases ATP production, ultimately resulting in neuronal death.

Potential Treatments of SBI after HICH

At present, a consensus has not been reached regarding SBI prevention and control after HICH. We always give priority to the treatment of the primary disease in clinical practice, and only perform symptomatic treatment when SBI occurs, which can lead to brain injury again. In order to search for a more effective prevention and control plan on the basis of current measures, the following are important.

Treatment of Fever after HICH

For fever, ice therapeutic caps and other physical cooling measures should be undertaken first. If there is an infection, the pathogen should be identified and appropriate countermeasures taken. Mayer et al. [16] and Kilpatrick et al. [17] reported that mild hypothermia treatment as soon as possible can prevent high fever and respiratory failure, on the basis of effectively relieving brain edema after HICH and reducing ICP [18, 19]. Liao and Peng [20] divided 60 patients into two groups, a test group given Dachengqi Decoction and a control group given conventional Western medicine, and found that the test group was superior to the control group in terms of defervesce and a lower neurologic impairment score. Some scholars [21] confirmed the above conclusions by combining traditional Chinese medicine (TCM) with mild hypothermia treatments.

Treatment of Hypotension after HICH

The key to controlling hypotension is the antihypertension opportunity [22] and making good use of antihypertensive drugs and frequent blood pressure screening. With respect to when to lower blood pressure, the Chinese guidelines for the management of acute intracerebral hemorrhage have proposed when to decrease the blood pressure, so the details need not be given here. When it comes to the current use of antihypertensive drugs after HICH, the guidelines [23] state that intravenous preparations, which have a quick effect and short half-life, are preferred. At the same time, it is necessary to continuously monitor blood pressure and to be careful with oral calcium channel blockers. For hypotension or relatively low blood pressure, fluid infusion, blood transfusion, and antishock treatment undertaken in a timely manner and providing symptomatic treatment are necessary. This can be combined with TCM to adjust blood pressure. TCM may prevent abrupt blood pressure fluctuations.

Treatment of Hypoxemia after HICH

Ensuring that the respiratory tract remains unobstructed is extremely important for HICH patients in the acute period, such as by keeping the mouth and nose clear, timely intubation to oxygen if the patient is experiencing poor ventilation function or hypoxemia, performing a tracheotomy and using a ventilator if necessary, and administering antibiotics. In recent years, hyperbaric oxygen therapy has been used more and more since brain tissue is particularly sensitive to oxygen. Hyperbaric oxygen improves the oxygen partial pressure through a variety of mechanisms to increase the tissue blood oxygen content. Many researchers [24–26] have reported that hyperbaric oxygen therapy as soon as possible after HICH can not only effectively prevent and cure hypoxemia, but also bring benefits to patients in terms of cure rate, quality of life, survival rate, prognosis, and rehabilitation.

Treatment of Hyperglycemia after HICH

Insulin is the first-choice treatment for hyperglycemia after HICH (blood glucose ≥ 10 mmol/L). Secondly, we must strengthen blood glucose monitoring and limit sugary liquid consumption. However, hyperglycemia caused by blood glucose regulating center injury due

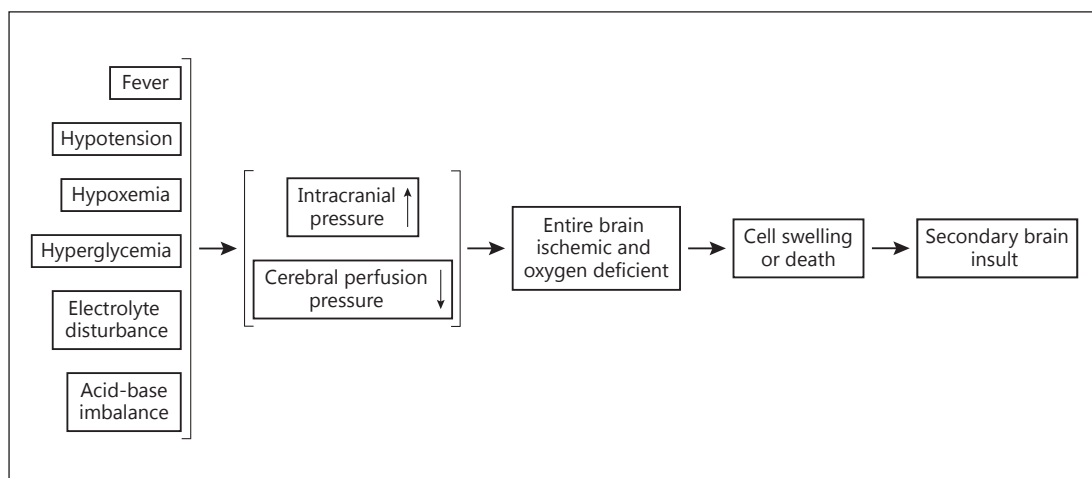


Fig. 1. Pathogenesis of secondary brain insult of hypertensive intracerebral hemorrhage.

to a brain stem hemorrhage can exist for a long period of time. Further research on the rational use of insulin to control this kind of hyperglycemia effectively still needs to be conducted.

Treatment of Electrolyte Disturbances and Acid-Base Imbalance after HICH

Cerebrovascular disease guidelines have not addressed targeted prevention and control measures concerning electrolyte disturbances and acid-base imbalance. Clinical studies mainly focus on signs and symptoms as well as laboratory indicators for symptomatic treatment and prevention of disease. Electrolyte disturbances after HICH are complex, easily confused with neurologic symptoms of HICH, easily neglected, and have a high fatality rate. Therefore, once they are found, they should be corrected in a timely manner. In addition, infusion time, length, type, speed, and volume are the keys to preventing and curing electrolyte disturbances. Chen et al. [27] reported that surgical minimally invasive treatment can reduce electrolyte disturbances in HICH patients. Acid-base adjustment focuses on the primary disease, protecting the important acid-base balance-lung function connection.

Summary

To summarize (Fig. 1), the essence of SBI after HICH is a secondary brain lesion on the basis of primary HICH. Fever, hypotension, hypoxemia, hyperglycemia, electrolyte disturbance, and acid-base imbalance after HICH eventually increase ICP, leading to a continual decline in CPP and cerebral hypoperfusion, causing irreversible pathological lesions in brain tissue. Once the CBF and the CPP have been decreased for as long as 6–8 h, the lesion will be irreversible. If the elevated ICP fails to be lowered, the CPP will continue to decrease, and then the entire brain will become ischemic and oxygen deficient. The lack of ATP causes a reduction in cell membrane pump function, calcium overload, and cell swelling or death. It is the final stage in the death of a neuron. As the pathogenetic factors and pathological mechanism of SBI gradually become more clear, the prevention and treatment of SBI after HICH will definitely be improved. However, clinical treatments for SBI after HICH are in the hysteric stage, so it is urgent to explore effective methods. Recently, a study found that Nao-Xue-Shu oral liquid has a markedly lower incidence of SBI, inhibits the accumulation of hematoma, improves the

absorbance of hemorrhage, eliminates the toxic stimulation of peripheral brain tissue, and inhibits the accumulation of inflammatory factors [28]. Chinese medicine has the distinctive function of modulating the body or dealing with diseases, including the treatment of brain problems [29, 30]. We are still unable to show how the ingredients pass through the blood-brain barrier, but they have been used in many countries for treating many diseases [31]. Thus, TCM intervention can be used as an important breakthrough in SBI, and TCM combined with Western medicine, conventional therapy in particular, may help bring SBI under control.

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