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Progress in Analgesic-Sedative Treatment in Perioperative Period of Hypertensive Intracerebral Hemorrhage

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Abstract

Hypertensive intracerebral hemorrhage (HICH) refers to intra cerebral hemorrhage at basal ganglia, thalamus, ventricle, cerebellum and brainstem in patients with history of explicit hypertension disease, excluding secondary cerebral hemorrhage caused by trauma, vascular structural disorders, coagulation disorders, hematologic diseases, systematic diseases and neoplastic diseases. HICH is characteristic of high morbidity, fatality rate, disability rate and recurrence rate. HICH is the most common type of spontaneous cerebral hemorrhage and various surgical interventions are one of the major treatments for HICH. Surgical treatment is to eliminate hematoma, relieve oppression of hematoma on surrounding brain tissues, lower intracranial pressure and alleviate secondary brain tissue damages, thus enabling to decrease fatality rate of patients and improve the long-term quality of life. Patients with HICH often may have different degrees of coma, pains, dysphoria, anxiety and delirium in the postoperative period. After central pivot was damaged, the sympathetic central excitability spreading is strengthened in the state of cortical inhibition, which also might be accompanied by paroxysmal sympathetic hyperexcitation syndrome to strengthen disease conditions of patients and thereby influence subsequent treatment. Several professional guidelines all recommend analgesic-sedative treatment as an important component of ICU therapy. However, it lacks support by large sample sized clinical research results of analgesic-sedative treatment of HICH in the postoperative period. This study analyzed literature concerning analgesic-sedative treatment of HICH in the postoperative period in recent years, aiming to guide specific clinical implementation.

Keywords

Hypertensive Intracerebral Hemorrhage, Postoperative Period, Analgesic-Sedative Treatment

1. Pathogenesis of Hypertensive Intracerebral Hemorrhage

Hypertension can cause pathological changes of general organs and blood vessels. Cerebral vessels develop retrogression and arteriosclerosis under long-term high pressure to adapt to hypertension. The wall of cerebral arterioles is thickened to resist high pressure and prevent the increase of the subsequent cerebral microcirculation perfusion pressure. All of these changes are particularly serious in arteriae perforantes at basal cerebral. Therefore, intracerebral hemorrhage is the collaborative result of anatomical features of cerebral vessels, pathological changes of blood vessel walls and a sudden increase of blood pressure [1].

Anatomical features of cerebral vessels: the wall of cerebral arterioles is relatively thin and there are a few medium membrane muscle fibers, without elastic fiber layer. The adventitia is significantly weaker than arteries of other organs. Moreover, basal cerebral perforating branches, such as lenticulostriate arteries and thalamic perforating branch are all originated from the terminal branch of the main blood vessels and most of them form an angular of 90˚ with the main blood vessels. Due to these anatomical features, intraluminal pressure is significantly higher than pressure of intracerebral blood vessels with the same diameter at other positions. Hence blood vessels become the predilection site of hypertensive intracerebral hemorrhage (HICH).

Pathological changes of blood vessel wall: the wall of cerebral arterioles develops hyaline change or fibroid degeneration and even local tiny hemorrhage, ischemia or necrosis due to hypertension. The inner elastic fiber layer is damaged to form small sacculated aneurysm or dissecting aneurysm. Such dissecting aneurysm is often seen in patients over 50 years old and it mainly distributes in basal ganglion, pons, white matter and cerebral perforator arteries. When the blood pressure increases suddenly, the microaneurysm breaks to cause cerebral hemorrhage.

Hypertension is the primary cause of pathological changes of arterial wall. When blood pressure increases suddenly, the weak points of the arterial wall are easy to develop rupture hemorrhage. Blood pressure transmits in the pulse way and thrombus is formed at rupture of arterial wall after hemorrhage. The arterial wall also becomes narrow due to oppression by hematoma and blood flow resistance increases, thus stopping hemorrhage automatically.

By analyzing pathogenesis of HICH, we found that blood pressure is the sole regulating factor in the postoperative period. The goal of controlling secondary hemorrhage in patients with HICH can be realized by controlling blood pressure in the postoperative period.

2. Significance of Analgesic-Sedative Treatment in Patients with HICH during Postoperative Period

It is reported by studies that postoperative sedative treatment is an independent factor that influence prognosis of craniotomy evacuation of hematoma in patients with HICH [2]. It can stabilize postoperative blood pressure effectively,

decrease the occurrence rate of postoperative agitation and occurrence rate of secondary hemorrhage, thus improving prognosis [2] [3].

Liu Jiansheng *et al.* [4] divided 70 cases of HICH into the treatment group (n = 35) and the control group (n = 35). Both groups were immediately transferred into NICU for intensive care treatment after operation. The control group applied treatments including dehydration, hemostasis, stomach protection, nerve protection and repair. The treatment group received intravenous pumping of mixture of sufentanil, propofol and midazolam as analgesic-sedative treatment in addition to treatments of the control group. Sedative agitation score (SAS), heart rate (HR), oxyhemoglobin saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure, dosage of hypotensor and occurrence rate of secondary hemorrhage of two groups at 1 h, 2 h, 4 h, 8 h, 12 h, 16 h, 24 h and 48 h after the operation were monitored. Results showed that there are statistical significant differences between the control group and the control group in term of SAS, SBP, DBP, HR, dosage of hypotensor and occurrence rate of secondary hemorrhage ($P < 0.05$). However, there's no statistical significant difference between two groups in SpO_2 ($P > 0.05$). This proves that the sufentanil, propofol and midazolam combined analgesic-sedative treatment in ICU is safe and effective to patients with HICH. It can control blood pressure stably, decrease occurrences of secondary hemorrhage and lower fatality rate of patients.

Liu Xiaojia [5] divided 150 patients who were administrated for HICH into two groups according to different treatments. The research group had 75 patients who received dexmedetomidine-remifentanil hydrochloride combined sedative treatment after evacuation of hematoma. The control group had 75 patients who used the midazolam-remifentanil hydrochloride combined sedative treatment after evacuation of hematoma. HR, mean arterial pressure (MAP), Richmond agitation sedation score (RASS) and Bispectral index (BIS) of two groups at 0 h, 6 h, 24 h and 48 h after the operation were observed. Moreover, occurrence rate of secondary cerebral hemorrhage and fatality rates of two groups were recorded. Results showed that HR and MAP of the research group are significantly lower compared to those of the control group at 6 h, 24 h and 48 h ($P < 0.05$). RASS and BIS of the research group are significantly lower than those of the control group. The research group shows lower occurrence rate of secondary hemorrhage and fatality rate than the control group. All of above differences between two groups have statistical significance ($P < 0.05$). Results indicate that dexmedetomidine-remifentanil hydrochloride combined sedative treatment can not only maintain stable blood pressure well after intracranial evacuation of hematoma and provide significant sedative effect, but also decrease the occurrence rate of secondary hemorrhage and fatality rate after operation.

Clinically, it is often to see unsatisfying antihypertensive efficacy by using hypotensor only after operation. It is still difficult to control blood pressure at the ideal level by increasing dosage of hypotensor only or using combined drugs. In

this case, adverse stimulation and sympathetic activation are important causes of HICH, including pain stimulation, agitation, anxiety and delirium as well as trachea intubation, retention catheterization, indwelling gastric tube and various nursing procedures. Analgesic-sedative treatment can eliminate or alleviate pains and physical discomfort of patients, decrease adverse stimulation and excessive excitation of the sympathetic nervous system, relieve or eliminate anxiety, agitation and even delirium of patients, prevent intervention of treatment by unconscious behaviors of patients, lower metabolism loads of organs, mitigate damages of organs, decrease various stress and inflammatory injuries, protect storage function of organs, and maintain homeostasis of body, thus decreasing blood pressure and intracranial pressure. The short-term mild sedation is also conducive to compliance of patients to treatment and nursing [6].

3. Postoperative Analgesic-Sedative Strategy and Mode to Patients with HICH

Now, the critical care pain observation tool (CPOT) and behavioral pain scale (BPS) are recommended to evaluate pains in patients who are in coma but have observable behaviors. Now, the common clinical subjective sedation scoring systems include Richmond agitation-sedation score (RASS), Riker sedation-agitation score (SAS) and bispectral index (BIS). Confusion assessment method for the ICU (CAM-ICU) or intensive care delirium screening checklist (ICDSC) is suggested for conventional delirium evaluation to patients who have RASS ≥ 2 and delirium-related risk factors. Both evaluation methods have relatively high sensitivity and specificity. It is suggested that the superficial sedation: RASS = −2 - +1 and SAS = 3 - 4; deep sedation: RASS = −3 - −4 and SAS = 2; combined administration of neuro-muscular blockers: RASS = −5 and SAS = 1 [7].

Analgesic-sedative treatment of patients with HICH shall observe the general principle for critical patients. Pain and discomfort are primary causes of agitation of most patients. Hence, it shall consider sedation treatment and correct abnormal physiology (e.g. hyoxemia, hypotension and hypoglycemia) firstly to critical patients. Analgesic treatment shall be the basis of sedation treatment.

In clinics, postoperative analgesic-sedative treatment to patients with HICH mainly refers to guideline of analgesic-sedative treatment for critical patients in ICU or for craniocerebral injury. Common sedation mode has programmed sedation, daily interrupted sedation and early target-oriented sedation. Different analgesic-sedative treatments have both advantages and disadvantages and can be used independently or collaboratively according to practical situation.

The programmed sedation is a sedation mode which is extensively used in clinics. It adjusts dosage of analgesic drug according to daily analgesic depth to realize the ideal analgesic goal. This proposes high requirements on nursing level and usually can only be implemented in ICU. The daily interrupted sedation observes changes of consciousness and disease conditions of patients by de-

creasing daily dosage gradually until stopping use of analgesic-sedative drugs, and then recovers the original administration of analgesic-sedative drugs. There's still controversy over daily interrupted sedation to patients with HICH. The dramatic changes of consciousness might induce increases in blood pressure and intracranial pressure, thus causing psychological stress [8] and even secondary hemorrhage. In particular, the benefits of daily interrupted sedation must be balanced with the risk of further cerebral hemodynamic deterioration upon sudden withdrawal of analgesic-sedative treatment in the acute phase. Patients who have risks of intracranial hypertension, receiving target body temperature management or continuous state of intractable epilepsy shall avoid daily interrupted sedation. It is suggested to withdrawing the sedation state gradually rather than suddenly. Early target-oriented sedation [9] was proposed by Shehabi in 2013 for the first time. Based on analgesia, sedative drugs are used for intervention in early stage and the superficial sedation shall be maintained within a period, without daily interrupted sedation. Meanwhile, it shall avoid or decrease the administration of benzodiazepines. Similar with programmed sedation, early target-oriented sedation relies on evaluation of bedside nurses too much and it incurs high nursing workloads.

4. Characteristics of Common Analgesic-Sedative Drugs to Patients with HICH

For patients with HICH, two basic principles shall be observed in selecting analgesic-sedative drugs. On one hand, drugs have no additional damages to brain tissues and they won't cause risks of increased intracranial pressure and decreased brain tissue perfusion. On the other hand, drugs have quick metabolism and the drug effect can be eliminated in a short time after withdrawal, thus enable to preventing a series of adverse reactions caused by accumulation in bodies.

Now, opioid is one of strong central analgesics and it is still the basic drug in pain management of patients in ICU. Common opioids in ICU include morphine, fentanyl, remifentanil, sufentanil, dihydromorphinone, butorphanol and dezocine. Since repeated administration of fentanyl is easy to accumulate in bodies, fentanyl is inappropriate as a drug for long-term analgesia treatment. Remifentanil and sufentanil are used more and more to patients in ICU in recent years. Adverse reactions of opioids mainly include respiratory depression, fall of blood pressure and weakening gastrointestinal peristalsis, which are particularly obvious in the aged.

Remifentanil: it is a fentanyl μ-type opioid receptor agonist and it mainly binds with α-1-acidoglycoprotein. It can be hydrolyzed quickly in tissues and blood, and acts in 1 - 3 min. However, the acting time of remifentanil is short and the half-life period is only 3 - 10 min, without causing liver and kidney injuries. Recent studies found that remifentanil can shorten duration of mechanical ventilation and length of stay in ICU significantly [10]-[15].

Sufentanil: it has very strong analgesic effect, which is 5 - 10 times that of fen-

tanyl. The half-life period reaches about 12h and individual dose difference is relatively large. The half-life period of distribution is short and the half-life period of metabolism is long. Long-term administration of sufentanil might prolong mechanical ventilation.

Benzodiazepines and propofol are still the basic drugs in current sedation treatment. Dexmedetomidine has mild sedation and analgesic effect through the effects of antagonistic central pivot and peripheral catecholamines. It has been proved by studies that dexmedetomidine has collaborative effect with other analgesic-sedative drugs to shorten mechanical ventilation and length of stay in ICU.

Midazolam is a benzodiazepine and can provide sedative-hypnotic, anti-anxiety, anti-convulsion and anti-epilepsy, central muscle relaxing, etc. As the drug with the strongest relative water solubility in benzodiazepines, midazolam acts in 3-5 min after intravenous injection. It has relatively short duration and high plasma clearance. With these characteristics, midazolam has high safety and small side effect to cardiovascular system. However, it often causes tachycardia [16] and may arrest respiration to some extent. Additionally, it has to note in clinics that 1% - 15% patients may develop contradiction effects after administration of midazolam, which are completely opposite symptoms with sedation, such as agitation, fear, anger and even autotomy [17] [18].

Propofol is a kind of alkyl group-based intravenous general anesthesia drug. It is characteristic of quick acting, short duration, quick awakening after withdrawal and dosage dependence in sedation depth. Propofol also can induce forgetting effect and anti-convulsion. It can decrease cerebral blood flow (CBF), intracranial pressure (ICP) and CMRO2. It can relieve increase of ICP as sedative treatment to patients with craniocerebral injury. Single injection of propofol can cause temporary respiratory depression, fall of blood pressure and bradycardia, especially in patients with poor cardiac reserve function and hypovolemia. Other adverse effects include hypertriglyceridemia, acute pancreatitis and striated muscle injuries. During administration of propofol, patients may suffer pains from peripheral intravenous injection. Hence, it usually applies the continuous slow intravenous dripping of propofol in clinics. Besides, some patients may develop propofol resistance after long-term administration.

Dexmedetomidine is a selective $\alpha 2$ receptor stimulant. It can mitigate sympathetic activation, calm down, resist anxiety and provide mild provides analgesic-sedative effects by inhibiting norepinephrine releasing from the nucleus ceruleus and through competitive binding with $\alpha 2$ receptor. However, it cannot resist convulsion.

Since dexmedetomidine doesn't act on the midbrain reticular ascending system and GABA receptors, patients are easier to awake and suffer less respiratory depression. Dexmedetomidine usually acts in 15 min after intravenous administration and the sedation peak occurs in 1 h after the intravenous administration. It can diffuse to periphery tissues and metabolized by liver quickly. For patients

with normal liver functions, the elimination half-time is about 3 h. For patients with severe hepatosis, clearance of dexmedetomidine is prolonged and dosage shall be decreased properly. Hypotension and bradycardia are the most common adverse reactions of dexmedetomidine. If intravenous administration is too quick, it might cause fluctuation of blood pressure and HR. Hence, attentions shall be paid to administration speed in ICU and the administration time can be prolonged properly if necessary. Moreover, dexmedetomidine has analgesic effect and it can decrease needs of opioids.

5. Conclusion

Analgesic-sedative treatment of patients with HICH in postoperative period is of great significance to prognosis of HICH. However, it still lacks high-level evidence-based medicine to guide postoperative analgesic-sedative treatment for HICH. Now, programmed sedation and early target-oriented sedation are applied frequently. Midazolam, dexmedetomidine, sufentanil and remifentanil are relatively ideal drugs. It is suggested to combine analgesic-sedative drugs according to individual schemes to realize good therapeutic effects and mitigate side effects caused by a high dosage of a drug.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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