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Research Progresses in Effects of Analgesics and Sedatives on Intracranial Pressure of Neurointensive Care Patients

Gang Yang

Department of Neurosurgery, Zhuji Affiliated Hospital of Wenzhou Medical University, Shaoxing, China
Email: tekeyang@sina.com

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Abstract

At present, there are some concerns and problems to treat neurointensive care patients by using analgesics and sedatives. Conditions of neurointensive care patients change quickly. For neurointensive care patients who cannot have auxiliary examination timely, clinicians judge intracranial conditions mainly through relevant monitoring devices and consciousness and pupil changes of patients. The use of analgesics and sedatives is limited due to worry about influences on consciousness evaluation and judgment and different degrees of inhibition on cardiovascular system and respiratory system. Common sedatives (e.g. benzodiazepines) and common analgesics (e.g. morphine, fentanyl and sufentanil) both may inhibit respiration. The specification often provides taboos for the use of drugs by patients with increase intracranial pressure (ICP) and craniocerebral injuries. Through literature review, the author analyzed influences of analgesics and sedatives on ICP of neurointensive care patients comprehensively.

Keywords

Neurointensive, Analgesics and Sedatives, Intracranial Pressure

1. Common Analgesics and Sedatives Used in Clinics for Neurointensive Care Patients

Now, Diazepam, Midazolam and Propofol are common sedatives in clinics. From the perspective of practical clinical applications, fast recovery and free adverse reaction of central nervous system are two important factors that must be considered when choosing drugs. Midazolam and Propofol have both characteristics and they are used mostly in neurointensive care patients. Other benzodiazepines

like Lorazepam are not appropriate for continuous administration of patients with severe craniocerebral trauma due to the longer half-life period.

Diazepam: It has anti-anxiety, sedation, anticonvulsion and muscle relaxation. Its advantages are fast-acting, mild cardiovascular responses, short half-life period, quick excretion and wide dosage range and reversible sedation by specific antagonist flumazenil. However, it is relatively easy to cause respiratory depression, hypotension, especially phlebophlogosis. High attentions shall be paid to sedation depth during administration. It is recommended to decrease dosage for long-term administration and decrease dosage slowly until drug withdrawal, aiming to decrease abstinence syndrome.

Midazolam: This is kind of water soluble sedative and fast-acting. Clinical administration shows dose-dependent hypnosis, anti-anxiety, anterograde amnesia and anti-spasm. It is a common sedative in clinics. Compared with Diazepam, Midazolam provides faster acting and longer duration. However, long-term administration also can cause complications and it is easy to produce fast tolerance, thus resulting in progressive growth dosage. It also might cause abstinence syndrome after drug withdrawal.

Propofol: It is a type of short-acting intravenous anesthetics belonging to alkyl acids. It can provide sedation, anti-anxiety, anti-convulsions, oblivion, very strong hypnosis and anesthetic action when the dosage is lower than the anesthetic dosage. It is lipid soluble and fast-acting. Propofol generally can bring patients into the sleep state in 40s. Due to very high lipid solubility and relatively low plasma concentration, Propofol is easy to run through the blood brain barrier (BBB) and hardly leaves drug accumulation, accompanied with low incidence rate of nausea and vomiting, short half-life period and quick recovery. Moreover, Propofol is applicable to patients with severe craniocerebral injury and mechanical ventilation since it can lower intracranial pressure (ICP) and decrease oxygen consumption and cerebral blood flow (CBF). Propofol has some adverse reactions, such as pains at injection point, respiratory depression, easy occurrence of Propofol infusion syndrome, hypertriglyceridemia, which may further cause pancreatitis and allergy. Long-term administration can increase complications significantly.

At present, opioids are accepted as one of powerful central analgesics and they are still the basic drugs in pain administration of patients in intensive care unit (ICU). Common opioids include morphine, fentanyl, Remifentanil, sufentanil, dihydromorphinone, butorphanol, dezocine, and so on. Repetitive administrations of fentanyl are easy to cause accumulation and it is inappropriate for long-term analgesia. Remifentanil and sufentanil are used more and more in patients with severe craniocerebral trauma.

Remifentanil: It is fentanyl μ-type opiate receptor agonist. It mainly binds with α-1-acidoglycoprotein and can be hydrolyzed quickly in tissues and blood. It acts in 1 - 3 min and has short duration. The half-life period is only 3 - 10 min, without causing liver and kidney damages. Recent studies found that Remifenta-

nil can shorten mechanical aspiration time and length of stay in ICU significantly.

Sufentanil: It has strong analgesic effect, which is 5 - 10 times that of fentanyl. The half-life period reaches about 12 h and the individual difference in dosage is significant. The half-life of distribution is short and the half-life of metabolism is long. Long-term administration can prolong time of mechanical aspiration.

Butorphanol Tartrate: It is an antagonist of opiates and acts on κ receptor. It has both analgesia and sedation effects, which are equivalent to those of fentanyl. It can decrease side reactions of opiates, such as erythema, pruritus, nausea and vomiting, addiction, etc. The respiratory depression is mild, which is only 1/5 of that of morphine. The peak effect can be realized with a dosage of 15 mg/70kg and analgesia is safer to weaning patients. It doesn't inhibit gastrointestinal peristalsis and causes no constipation and immunosuppression to long-stay patients. Moreover, it has no obvious influences on heart rate and blood pressure.

Dexmedetomidine hydrochloride: It is a short-acting and high-selectivity α2 receptor agonist and it is also a relatively new sedative and analgesia drug. Dexmedetomidine hydrochloride has dose-dependent sedative-hypnotic, analgesia and sympathetic nerve activity inhibition, but has small influences on circulatory function, without respiratory depression. It is the sole sedative that can awaken patients during operation at present. During sedation, it also can maintain conscious of patients, without obvious respiratory depression. Moreover, haemodynamics are easy to be monitored and controlled. Therefore, Dexmedetomidine is the ideal sedative of patients with postoperative agitation and it can decrease incidence rate and severity of delirium. Moreover, it can provide great analgesic effect, but the definite mechanism still remains unknown. Compared with Midazolam, Dexmedetomidine has small influences on GCS scores of patients, which is known as sober sedation. It won't influence conscious state of patients. Doctors can judge consciousness of patients at any time and adopt effective emergency aid measures to increase survival rate and decrease disability rate of patients. In clinics, the combined administration of Dexmedetomidine and Butorphanol Tartrate can achieve better analgesic and sedative effects, while adverse effects are decreased [1] [2] [3] [4] [5].

2. State of the Art

Liu *et al.* [6] found that Sedative and analgesic treatments in patients with severe TBI at NICU administered within 24 h post operation can reduce their ICP values and fluctuations. The clinical data of 60 patients with severe TBI admitted to Neurosurgical Intensive Care Unit (NICU) of Renji Hospital, School of Medicine, Shanghai JiaoTong University from September 2018 to May 2019 were retrospectively analyzed in this study. All patients initially underwent intraventricular ICP monitoring probe implantation, which was followed by craniotomy, hematoma removal and craniectomy. According to whether sedative and analgesic treatment based on conventional treatment was administered within 24

hours post operation, the patients were divided into two groups: sedation and analgesia group (30 cases) and routine treatment group (30 cases). We compared the clinical data and ICP related indexes between the two groups. ICP observations included the average value of ICP at 4 time points (6, 12, 18, 24 hours), mean ICP amplitude (MWA), cerebrovascular pressure response index (PRx), and ICP fluctuations per 6 hours. Results There were no significant difference in sex, age, cause of injury, Glasgow coma scale (GCS) score at admission, injury time, injury site, or type of craniocerebral injury between the two groups (all $P > 0.05$). There was no significant difference in initial ICP between the two groups ($P > 0.05$). The ICP values in the two groups were normal at the end of operation, and there was no significant difference between the two groups ($P > 0.05$). The ICP of patients in the 6-, 12-, 18-and 24-hour groups were normal after operation, while the average ICP, MWA and PRx of the sedation group were lower than those in the routine treatment group (all $P < 0.05$). Within 24 hours post operation, the ICP fluctuations per 6 hours in sedation and analgesia group was lower than those in routine treatment group (all $P < 0.05$).

Xu *et al.* [7] found that there was no significant difference in ICP between patients with severest TBI before and after sedation and analgesia ($P > 0.05$). There was a significant difference in ICP changes before and after sedation and analgesia in patients with severe TBI ($P < 0.05$). Conclusion: Analgesia and sedation are significantly correlated with intracranial pressure fluctuations after craniotomy operation for severe TBI. In severe TBI group, safe and stable ICP can be obtained by controlling sedation and analgesia.

Many clinical studies [8]-[13] agreed that treatment of analgesics and sedatives may influence ICP of patients with severe craniocerebral trauma to some extent. They can decrease ICP effectively and make ICP of patients stabilized gradually, thus increasing therapy safety and promote recovery of patients.

Chen *et al.* [14] study clinical effect of sedation analgesia treatment in patients with hypertensive intracerebral hemorrhage after operation. 218 patients with hypertensive cerebral hemorrhage were randomly divided into two groups, Sufentanil + Dezocine + Midazolam had been applied to postoperative sedation analgesia treatment in experiment group, the control group used midazolam only, to observe the therapeutic effect of two groups. The sedation-agitation score, the number of patients with dangerous blood pressure, intracranial pressure, national institutes of health stroke scale of postoperative 72 h, rebleeding rate within 48 h, 7 days' mortality and adverse reaction of experimental group were all lower than control group, the difference had statistical significance ($P < 0.05$). In patients with hypertensive intracerebral hemorrhage after operation, sufentanil + dezocine + midazolam could reduce postoperative dysphoria, stabilize postoperative blood pressure and ICP, protect neurological function, meanwhile, reduce the rebleeding rate, mortality and adverse reaction. It is worth clinical application and promotion.

Li Jian [15] provided different analgesic and sedative treatment schemes to

two groups of patients. Specifically, the conventional group was treated by Midazolam, while the observation group was provided with combination analgesia of sufentanil and dezocine in addition of Midazolam. The differences between two groups in postoperative sedative agitation score and ICP detection values were compared. According to survey on analgesic effects of the chosen patients, the postoperative sedative agitation score of the observation group was significantly lower compared to that of the conventional group, and ICP detection value was significantly better ($P < 0.05$), showing statistical significant differences. In conclusion, analgesia of Sufentanil Dezocine based on Midazolam to patients with hypertensive cerebral hemorrhage after operation can relieve pains effectively and improve ICP.

Yang *et al.* [16] pointed out that ICU continuous deep sedation and analgesia can significantly reduce the postoperative intracranial pressure and incidence of complications of patients with spontaneous intracerebral hemorrhage, which is conducive to improving patients' prognosis

Liu Jiansheng *et al.* [17] pointed out that the analgesic and sedative treatment of sufentanil, Propofol and Midazolam to patients with hypertensive cerebral hemorrhage after operation is safe and effective. It can control blood pressure steadily, decrease occurrence of secondary hemorrhage and lower fatality rate of patients. Girard F *et al.* [18] pointed out that moderately deep propofol sedation does not result in a higher ICP than no sedation in patients undergoing stereotactic brain tumor biopsy.

3. Brain Protective Effect of Analgesics and Sedatives in Neurointensive Care Patients and Their Influences on ICP

Severe neurologic symptoms, especially craniocerebral trauma, are a continuous strong noxious stimulus and their influences on patients involve various aspects, such as cardiovascular system, respiratory system, gastrointestinal system, endocrinium system, immune system and clotting mechanism. Pains can not only excite the sympathetic nervous system and cause stress responses, but also induce releasing of various proinflammatory factors in bodies. Excessive expressions of these cell factors can produce toxicity to nerve cells, thus resulting in cell swelling and deaths, breaking BBB and inducing or intensifying encephaledema. Moreover, these can induce expression of abundant other inflammatory mediators indirectly, thus causing secondary craniocerebral injury. Effective analgesic and sedative treatments can inhibit occurrences of stress responses obviously, decrease cerebral oxygen metabolism rate, improve cerebral blood flow, strengthen tolerance of brain tissues to ischemia and anoxia, and adjust supply and demands of various substances automatically.

According to literature review, analgesics and sedatives lower ICP through following aspects: 1) it decreases cerebral oxygen metabolism rate, which will decrease cerebral blood volume accordingly and lower ICP; 2) it relieves pains and anxiety, lowers arterial hypertension and increases ICP sharply; 3) it in-

creases tolerance to trachea cannula, decreases cough reflex, and avoids increasing intrathoracic, which decreases countercurrent in jugular veins, thus leading to high cranial pressure. Moreover, combination of antiepileptic drug in neurosurgical intensive care unit (NICU) can decrease epileptic seizure and control continuous state of epilepsy. Reasonable sedation and analgesia treatment also can decrease nursing risks of patients caused by self-drawing of air tube, stomach tube, electrocardiograph monitoring and artery or vein ducts due to agitation. For some critical patients with agitation, delirium and mechanical respiration, sedation, analgesia and muscle relaxing are essential parts in treatment, which can decrease man-machine counteraction during mechanical respiration. These also can decrease discomfort brought by anxiety, agitation, fear and pain because of surrounding physical environmental stimuli and iatrogenic operation in NICU.

Of course, respiratory depression of patients with severe craniocerebral trauma and without mechanical respiration during the administration of analgesics and sedatives must be observed carefully. Due to reduction of breathing dynamics, CO_2 retention is intensified, which further increases ICP. It is necessary to pay close attentions to ICP of these patients as well as symptoms of increasing ICP. During administration of analgesics and sedatives, high attentions shall be paid to blood pressure. It has to prevent excessive low blood pressure to cause insufficient cerebral perfusion pressure (CPP).

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Conflicts of Interest

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

References

[1] Wan, J., Fan, Q., Fan, C.H., *et al.* (2020) Effects of Combined Administration of Dexmedetomidine Hydrochloride and Butorphanol Tartrate on Stress State, NPAS4 and NSE of Old Patients with Craniocerebral Trauma. *Journal of Clinical and Experimental Medicine*, **19**, 2037-2041.

[2] Wang, B.L., Wang, H.X., Zhou, H.X., *et al.* (2018) Analgesia and Sedation Effect Observation of Dexmedetomidine-Butorphanol Combination in Patients with Hypertensive Intracerebral Hemorrhage. *Chinese Journal of Clinical Neurosurgery*, **23**, 792-794.

[3] Zhang, X.F., Yin, Z.W., Wu, W., *et al.* (2021) Effect Evaluation of Butorphanol-Dexmedetomidine Combination in Patients with Craniocerebral Trauma in ICU. *Chinese and Foreign Medical Research*, **19**, 47-50. https://doi.org/10.4236/cm.2021.123006

[4] Zhou, Q.Y., Liu, Y., Gao, L., *et al.* (2021) Application Effects of Different Doses of Butorphanol Combined with Dexmedetomidine in Patients with Severe Craniocerebral Trauma. *Henan Medical Research*, **30**, 1178-1181.

[5] Huang, X.L., Kong, B., Fu, Y.Y., *et al.* (2020) Evaluation of Analgesic Effect of Butorphanol-Dexmedetomidine Combination in Patients with Craniocerebral Trauma. *Leading Medicines*, **10**, 110-111.

[6] Liu, P.F., Feng, J.F., Wang, W.F., *et al.* (2020) Effect of Analgesic and Sedative Treatments on Intracranial Pressure in Patients with Severe Traumatic Brain Injury. *Chinese Journal of Neurosurgery*, **36**, 1026-1029.

[7] Xu, F., Shen, L.J., Zhong, X.M., *et al.* (2018) Effects of Sedation and Analgesia on Postoperative Intracranial Pressure in Patients with Severe Traumatic Brain Injury. *Chinese Journal of Neurotraumatic Surgery* (*Electronic Edition*), **4**, 276-278.

[8] Zhang, M., Hu, Y.L., Zhen, H., *et al.* (2019) Effects of Analgesics and Sedatives on ICP of Patients with Severe Craniocerebral Injury. *Clinical Research*, **27**, 110-112.

[9] Lu, Z.Q. (2016) Effects of Analgesics and Sedatives on ICP and Curative Effects in Patients with Traumatic Intracranial Hypertension in ICU. *Medical Theory and Practice*, **29**, 3039-3040.

[10] Zhen, X.Y. (2016) Effects of Analgesics and Sedatives on Curative Effects and ICP in Patients with Traumatic Intracranial Hypertension in ICU. *Electronic Journal of Clinical Medicine Literature*, **3**, 7961.

[11] Zhuang, M.Z. (2014) Effects of Analgesics and Sedatives on ICP and Curative Effects in Patients with Traumatic Intracranial Hypertension in ICU. *China Practical Medical*, No. 34, 146-147.

[12] Wu, Y.F. (2015) Effects of Analgesics and Sedatives on ICP and Curative Effects in Patients with Traumatic Intracranial Hypertension in ICU. *Contemporary Medicine*, No. 30, 60-61.

[13] Wu, Z.H. and Song, Q. (2014) Effects of Analgesics and Sedatives on ICP and Curative Effects in Patients with Traumatic Intracranial Hypertension in ICU. *Journal of Modern Integrated Chinese and Western Medicine*, **23**, 732-733.

[14] Chen, X.G., Li, W.L., Wang, K.P., *et al.* (2017) Clinical Effect of Sedation Analgesia Treatment in Patients with Hypertensive Intracerebral Hemorrhage after Operation. *Medicine and Philosophy*, **38**, 44-47.

[15] Li, J. (2019) Clinical Effect of Post-Operative Analgesics and Sedatives in Patients with Hypertensive Cerebral Hemorrhage. *Journal of General Stomatology* (*E-Version*), **6**, 170-171.

[16] Yang, M.X., Lu, W.T., Lai, J.L., *et al.* (2019) Observation on Curative Effect of ICU Continuous Deep Sedation Analgesia on Reducing the Postoperative Intracranial Pressure of Patients with Spontaneous Intracerebral Hemorrhage. *Clinical Medical & Engineering*, **26**, 607-608.

[17] Liu, J.S., Zhang, Y.J., Song, D.G., *et al.* (2019) Analysis on Curative Effect of Post-Operative Analgesics and Sedatives in Hypertensive Cerebral Hemorrhage. *Zhejiang Trauma Surgery Department*, **24**, 1042-1043.

[18] Girard, F., Moumdjian, R., Boudreault, D., *et al.* (2004) The Effect of Propofol Sedation on the Intracranial Pressure of Patients with an Intracranial Space-Occupying Lesion. *Anesthesia & Analgesia*, **99**, 573-577. https://doi.org/10.1213/01.ANE.0000133138.86133.38