Korean J Neurotrauma. 2023 Jun;19(2):185-194
https://doi.org/10.13004/kjnt.2023.19.e19
pISSN 2234-8999·eISSN 2288-2243

KJNT

Review Article

Deep Sedation in Traumatic Brain Injury Patients

Yoon-Hee Choo [1], **Youngbeom Seo** [2], **and Hyuk-Jin Oh** [3]

[1]Department of Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Neurosurgery, Yeungnam University Hospital, Yeungnam Universtiy College of Medicine, Daegu, Korea
[3]Department of Neurosurgery, Soonchunhyang University Cheonan Hospital, College of Medicine, Soonchunhyang University, Cheonan, Korea

Received: Feb 28, 2023
Revised: Apr 3, 2023
Accepted: Apr 4, 2023
Published online: May 31, 2023

Address for correspondence:
Youngbeom Seo
Department of Neurosurgery, Yeungnam University Hospital, Yeungnam Universtiy College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea.
Email: nsybseo@gmail.com

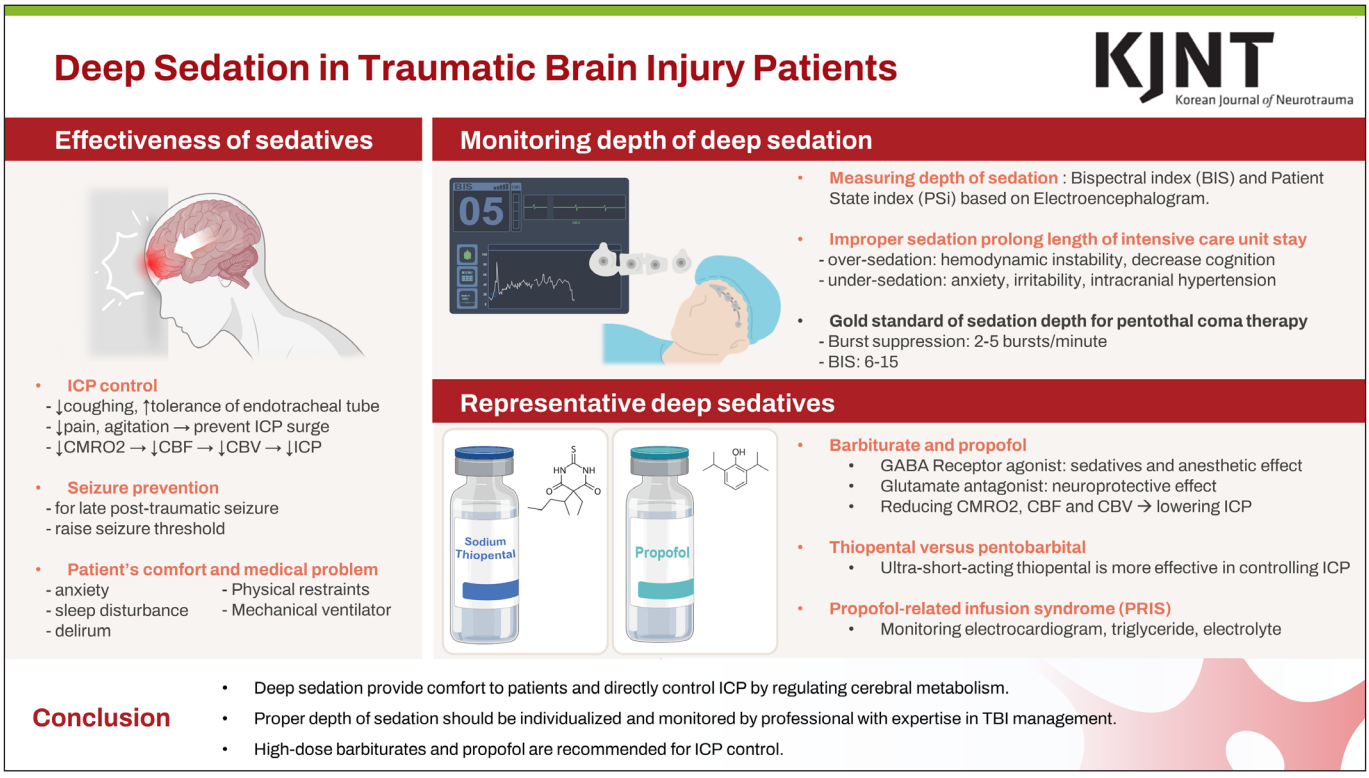
Hyuk-Jin Oh
Department of Neurosurgery, Soonchunhyang University Cheonan Hospital, College of Medicine, Soonchunhyang University, 31 Suncheonhyang 6-gil, Dongnam-gu, Cheonan 31151, Korea.
Email: funnylife@schmc.ac.kr
schnsohj@gmail.com

ABSTRACT

Traumatic brain injury (TBI) is one of the leading causes of mortality and disability in adults. In cases of severe TBI, preventing secondary brain injury by managing intracranial hypertension during the acute phase is a critical treatment challenge. Among surgical and medical interventions to control intracranial pressure (ICP), deep sedation can provide comfort to patients and directly control ICP by regulating cerebral metabolism. However, insufficient sedation does not achieve the intended treatment goals, and excessive sedation can lead to fatal sedative-related complications. Therefore, it is important to continuously monitor and titrate sedatives by measuring the appropriate depth of sedation. In this review, we discuss the effectiveness of deep sedation, techniques to monitor the depth of sedation, and the clinical use of recommended sedatives, barbiturates, and propofol in TBI.

Keywords: Deep sedation; Hypnotics and sedatives; Brain injuries, traumatic; Critical care

GRAPHICAL ABSTRACT



ORCID iDs

Yoon-Hee Choo
https://orcid.org/0000-0002-6077-6893
Youngbeom Seo
https://orcid.org/0000-0001-5568-3636
Hyuk-Jin Oh
https://orcid.org/0000-0001-7189-1267

Conflict of Interest

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings described in this paper.

INTRODUCTION

Deep sedation is widely used in the treatment of patients with traumatic brain injury (TBI) to control intracranial hypertension in the acute phase, as well as to address medical problems such as seizures, agitated behavior, sleep disorder, and delirium. It also alleviated discomfort related to anxiety and pain.[8,21,30,33] It is important to carefully monitor and titrate the depth of sedation by medical professional with expertise in TBI management, as over-sedation can result in negative outcomes such as prolonged cognitive dysfunction, hemodynamic instability, and ventilator-associated pneumonia.[36,37,41,49] Bispectral index (BIS) and patient state index (PSI) based on electroencephalogram are the most widely used devices for measuring sedation depth.[2] As neurological examination can be challenging in patients with TBI undergoing deep sedation, it is crucial to utilize monitoring devices like pupilometer or intracranial pressure (ICP) measurement to supplement the assessment of neurological function. In particular, propofol and barbiturates are recommended for patients with TBI to control intracranial hypertension.[4] Sedatives effectively control ICP by reducing cerebral metabolic rate of oxygen and cerebral blood flow.[33,36,37,49] However, inappropriate use of sedatives can lead to fatal complications such as hemodynamic instability, prolonged cognitive impairment, and propofol-related infusion syndrome.[10,20,26,32,38] Therefore, sedative treatment should be performed under professional supervision.

Herein, the rationale for using deep sedation in the treatment of TBI, the monitoring of the appropriate depth of sedation, and the clinical use of sedatives will be discussed.

https://doi.org/10.13004/kjnt.2023.19.e19

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional review board of our institute approved this study. Informed consent was waived for the retrospectively studied subjects because our study did not adversely affect their rights and welfare. Participants or the legal guardians of participants in the newly developed bundle protocol group provided written informed consent prior to study enrolment.

EFFECTIVENESS OF SEDATIVES IN TBI

ICP control

When intracranial hypertension occurs in TBI patients, cerebral perfusion pressure (CPP) decreases leading to a possible decrease in cerebral blood flow (CBF).[18] If ICP is not appropriately controlled, sedatives are required to minimize the risk of secondary brain injury. By suppressing cough and improving the tolerance against the endotracheal tube, it is possible to prevent an increase in intrathoracic pressure which can lead to an increase in intracranial pressure.[36,37]

By alleviating pain and anxiety and managing agitation, it can help prevent arterial hypertension often associated with surges in ICP.[36,37] First of all, a comfortable environment should be established using non-pharmacological methods, including reducing noise levels, managing lighting to facilitate sleep, providing explanations about the patient's condition, and minimizing the unnecessary use of restraints. The use of appropriate and sufficient analgesics can mitigate the side effects of sedatives, such as hemodynamic instability and metabolic disorders, by reducing the dosage of sedatives and concurrently alleviating pain and reducing ICP.[8,16,29,36] Moreover, this practice has the potential to decrease the length of intensive care unit stay and ventilator days, and to enhance achievement of sedation goals.[8,39,45] For example, the simultaneous use of remifentanil as an analgesic and propofol as a sedative is commonly used to manage intracranial hypertension in TBI patients.[36,39] However, if sedatives suppress breathing and cause carbon dioxide retention, it may result in cerebral vasodilation and increase ICP, particularly when autoregulation is not functioning properly. Hence, continuous monitoring of carbon dioxide levels is necessary. Moreover, certain sedatives such as barbiturate and propofol can enhance CPP by controlling CBF and cerebral blood volume (CBV), and reducing cerebral metabolic rate of oxygen ($CMRO_2$), which in turn improves intracranial hypertension.[33,36,37,49]

Seizure control

When brain damage occurs, it is difficult to maintain CBF and falls into a state of energy depletion, and as sodium and potassium alteration occurs based on the cell membrane, the secretion of glutamate increases. As a result, the seizure threshold is lowered, and the apoptosis pathway is activated by seizures, leading to neuronal death.[19,24] Therefore, preventing and controlling seizures is a very important issue in patients with brain damage. Post-traumatic seizures after severe TBI are common. The incidence of clinical post-traumatic seizure is 12%, and that of subclinical post-traumatic seizure detected on electroencephalogram (EEG) is 20%–25%.[4] Seizure leads to increase cerebral metabolism, causing a mismatch with oxygen delivery.[19,24] Early post-traumatic seizure occurring within the first week after trauma is a risk factor for late post-traumatic seizure occurring a week later.[52] Early post-traumatic seizure can be controlled by using anti-epileptic drugs, whereas, continuous use of anti-epileptic drugs is not effective in preventing or reducing the

https://doi.org/10.13004/kjnt.2023.19.e19

risk of developing late post-traumatic seizure.[47,50] Sedation can prevent and reduce the risk of late post-traumatic seizure. Several studies reported that phenobarbital and midazolam as sedatives raise seizure threshold and reduce the incidence of late post-traumatic seizure.[3,12,34,42,50]

Patient's comfort and medical problem

Patients admitted to an intensive care unit often experience anxiety due to the unpleasant nature of their surroundings. Mechanical ventilation and invasive treatments can exacerbate pain and anxiety, leading to the development of sleep disorders, delirium, and poor prognosis, including an increased risk of post-traumatic stress disorder and mortality.[10,54] Delirium is a prevalent condition affecting 50%–80% of severely ill patients, leading to acute cerebral dysfunction and adverse outcomes such as increased mortality, prolonged hospitalization, higher medical expenses, and long-term cognitive impairment similar to dementia.[10,20,32] Patients with neurological conditions are at higher risk of delirium due to exposure to multiple precipitating factors such as surgery, admission to an intensive care unit, physical restraints, mechanical ventilation, pain, and sleep disorders in addition to their primary neurological disease.[20,32] Appropriate sedation can help reduce the stress response, create a more comfortable environment, and control some of the factors that contribute to long-term health issues, such as pain, sleep disturbance, delirium, and seizures.[32]

MONITORING DEPTH OF DEEP SEDATION IN TBI

The proper depth of sedation in TBI depends on several factors, including severity of injury, a patient's medical condition, and the presence of other injuries. The proper depth of sedation relieves pain and anxiety, controls delirium, as well as controls brain edema so that ICP could be managed.[36] Over-sedation can lead to unfavorable outcomes such as respiratory depression, hemodynamic instability, long-term decrease in cognitive function and have limitation of neurologic assessment. Under-sedation causes anxiety, agitation, irritability in patients and intracranial hypertension. Both of improper depth of sedation prolong length of intensive care unit stay, and increase medical costs. The proper sedation in TBI should be individualized and monitored by professional with expertise in TBI management, considering the patient's individual medical conditions and needs. The depth of sedation should be continuously monitored and adjusted as needed.

In intensive care unit, the depth of sedation is measured by Richmond Agitation-Sedation Scale.[11] However, in the case of brain-injured patients, there are limitations in its application due to the characteristics of the disease. EEG-based mechanical devices such as BIS and PSI can measure the depth of sedation in brain-injured patients. Both BIS and PSI provide real-time information on the level of consciousness and sedation by expressing the suppression ratio as a number. In the case of catastrophic brain injury or brain death, the suppression ratio is almost 100%, and the BIS and PSI values are zero.[2] When measuring the suppression ratio, BIS measures only the EEG signal, while PSI comprehensively measures various physiological variables such as electromyogram (EMG) and heart rate.[2,9] Therefore, it is important to avoid making decisions based solely on BIS values.

However, in severe TBI patients where the impact of EMG is minimal, the BIS value correlates quite well with level of consciousness and depth of sedation.[28,44,48] Mahmood et al.[28] reported that BIS values have a significant correlation with initial Glasgow Coma Score and can assist in the early detection of brain death with severe acute TBI. Furthermore, the relationship between

https://doi.org/10.13004/kjnt.2023.19.e19

the number of bursts/minute on the EEG, the suppression ratio, and the BIS value during pentothal coma therapy (PCT) has been proven.[5,44,48,51] In PCT to reduce ICP to below 15mmHg, it has been demonstrated that when target burst suppression reached 3–5 burst/minute, BIS was 15 and suppression rate was 71% in adult patients,[44] while BIS was 14 and suppression ratio was 75% in pediatric patients.[48] There is a lack of consensus on the number of bursts/minute that is appropriate as the gold standard for PCT, however, it is commonly set as 2–5 bursts/minute.[5,44,46,48,51] In 2008, Cottenceau et al.[7] defined a word 'burst' as a period of electric activity interspersed with at least a second of suppression, and demonstrated a significant correlation between suppression ration on EEG and BIS value not only on the target BIS values but also on the entire range of BIS values from zero to 100 and suggested a guideline for PCT titration. They recommended the rate of barbiturate infusion might be decreased if BIS is <6 or increased if BIS is >15.[7] There are relatively few studies on optimal PSI value during PCT, however there is a report that BIS and PSI values show a high correlation of 0.8455 in sedation using propofol.[40]

REPRESENTATIVE DEEP SEDATIVES IN TBI

In the 4th TBI guidelines, high-dose barbiturates and propofol are recommended for ICP control.[4] Although there are other sedatives available for ICP management, due to a lack of evidence regarding their use, the choices of drug selection and dosages are diverse among physicians.[15] Compared to propofol, midazolam has lower hemodynamic stability.[37] However, it is less effective in reducing $CMRO_2$, CBF, and ICP, and is associated with delayed awakening,[37] prolonged intensive care unit stay and mechanical ventilation, and increase risk of delirium and post-traumatic stress disorder.[13,39,43,53] Therefore, there are limitations to using midazolam as a first-line drug for intracranial hypertension in TBI patients. Dexmedetomidine, an β-2 agonist, is a drug suitable for mild sedation and is useful for patients who exhibit agitation and delirium, however it has limited effects on managing ICP and CBF.[37] Hence, this article focus on the 2 recommended sedatives in TBI, barbiturate and propofol.

Barbiturate

According to the TBI guidelines by Brain Trauma Foundation, 'administration of barbiturate to induce burst suppression as prophylaxis is not recommended.' Because there is no significant difference in mortality or Glasgow Outcome Scale, and 'high-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment.' With the evidence that lower ICP had higher likelihood of survival for responders to treatment.[4] Several studies have reported that the survival rate is superior to barbiturate coma therapy for severe intracranial hypertension.[25,27] Barbiturate is a β-aminobutyric acid receptor agonist, which exhibit the effect of sedation and anesthesia, also has a neuroprotective effect as a glutamate antagonist.[6] On the premise that carbon dioxide reactivity is preserved during barbiturate coma therapy, not only CBV is reduced through a significant decrease in CBF, but also $CMRO_2$ is reduced, which has the effect of lowering ICP.[6,31,35] Thiopental, an ultra-short acting drug with a half-life of 3–18 hours, and pentobarbital, a short-acting drug with a that of 15–50 hours, are representative barbiturates used in barbiturate coma therapy.[6] After intravenous administration of the two drugs to rat, the concentration of the drugs in the serum and brain was measured.[14] Thiopental, which has better lipid solubility, was confirmed that the brain and serum concentration rapidly increased and was distributed and fell to the plateau level within minutes and it was interpreted that the effective level was quickly reached at the start of barbiturate coma therapy to control initial intracranial hypertension. In contrast, pentobarbital not only took more time for this process,

https://doi.org/10.13004/kjnt.2023.19.e19

but also had a strong tendency to maintain its concentration without dropping after reaching the plateau level. It is related to hemodynamic instability. In a randomized controlled trial conducted on 44 patients with TBI, the patients were divided into 2 groups, thiopental and pentobarbital.[41] The study found that the thiopental group was more effective in controlling ICP while the incidence of side effects such as hemodynamic instability and infections was similar between the two groups.[41] However, in terms of mean blood pressure reduction and inotropic demands, the thiopental group was found to be superior.[41]

Pentobarbital is recommended to administrate as a loading dose of 10 mg/kg over 30 minutes, followed by a maintenance dose of 1–3 mg/kg/hr to induce burst suppression on the EEG.[2] When discontinuing barbiturate coma therapy, it is recommended to monitor ICP, brain tissue oxygenation ($PbtO_2$), and mean blood pressure, and gradually decrease the dose by 0.5 mg/kg/hr every 6 hours.[2] According to research conducted with thiamylal, which is very similar to thiopental, a fixed dose of 3.0mg/kg/hour lead to toxic level within 24–48 hours, and when combined with hypothermia treatment, a more rapid increase in serum level was observed. Therefore, a step-down method is recommended with doses of 3-2-1.5-1.0 mg/kg/hour every 24 hours to avoid reaching toxic levels. Ultimately, monitoring of BIS, raw EEG, and serum barbiturate level should be performed.[23]

Propofol

According to the TBI guidelines by Brain Trauma Foundation, propofol is recommended for the control of ICP, not for improvement in mortality or 6-month outcomes.[4] Propofol, like barbiturate, also acts as a β-aminobutyric acid receptor agonist and glutamate antagonist.[1,36,37] It has dose-dependent EEG suppression effect and reduce ICP through CBF and $CMRO_2$ coupling by preserving cerebrovascular autoregulation.[22,37,49] Van Hemelrijck et al.[49] reported that as the dose of propofol increased, there were significant decrease in CBF and mean blood pressure. Propofol protects astrocytes from oxidative stress caused by acting at various stages of inhibiting lipid peroxidation and apoptosis leading to cell death.[1,17]

However, prolonged infusion of propofol requires caution in its use because it can cause rare but fatal complications propofol-related infusion syndrome (PRIS) as well as hemodynamic instability. PRIS is characterized by inducing an adenosine triphosphate depletion state by causing impairment of β oxidation in the mitochondria, which leads to rhabdomyolysis-induced renal failure, hyperkalemia, and cardiac dysfunction ultimately resulting in cardiovascular collapse and death.[26,38] Specifically, TBI increases the risk of PRIS, and the risk becomes higher when the dose exceeds 4 mg/kg/hr for more than 48 hours.[26,38] Therefore, greenish-colored urine, lipid such as triglyceride and electrolyte serum levels, and electrocardiogram should be monitored intensively during propofol infusion. When PRIS is suspected, administration of propofol and lipid preparations should be discontinued immediately.[26,38]

CONCLUSION

Deep sedative treatment not only helps regulate intracranial hypertension properly by directly acting on the brain during the acute phase of TBI, but also mitigates medical issues associated with brain damage such as seizures and delirium, and improves patient's comfort for quality intensive care. However, inadequate or excessive depth of sedation can lead to various complications. Therefore, it is crucial for experts in TBI care to diligently and continuously monitor and titrate the depth of sedation.

https://doi.org/10.13004/kjnt.2023.19.e19

ACKNOWLEDGMENTS

Due to nature of this study, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

REFERENCES

1. Adembri C, Venturi L, Pellegrini-Giampietro DE. Neuroprotective effects of propofol in acute cerebral injury. **CNS Drug Rev** 13:333-351, 2007
PUBMED | CROSSREF
2. Bader MK, Arbour R, Palmer S. Refractory increased intracranial pressure in severe traumatic brain injury: barbiturate coma and bispectral index monitoring. **AACN Clin Issues** 16:526-541, 2005
PUBMED | CROSSREF
3. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. **Neurocrit Care** 17:3-23, 2012
PUBMED | CROSSREF
4. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. **Neurosurgery** 80:6-15, 2017
PUBMED | CROSSREF
5. Cordato DJ, Herkes GK, Mather LE, Gross AS, Finfer S, Morgan MK. Prolonged thiopentone infusion for neurosurgical emergencies: usefulness of therapeutic drug monitoring. **Anaesth Intensive Care** 29:339-348, 2001
PUBMED | CROSSREF
6. Cordato DJ, Herkes GK, Mather LE, Morgan MK. Barbiturates for acute neurological and neurosurgical emergencies--do they still have a role? **J Clin Neurosci** 10:283-288, 2003
PUBMED | CROSSREF
7. Cottenceau V, Petit L, Masson F, Guehl D, Asselineau J, Cochard JF, et al. The use of bispectral index to monitor barbiturate coma in severely brain-injured patients with refractory intracranial hypertension. **Anesth Analg** 107:1676-1682, 2008
PUBMED | CROSSREF
8. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the icu. **Crit Care Med** 46:e825-e873, 2018
PUBMED | CROSSREF
9. Drewnowska O, Turek B, Lisowska B, Short CE. Preliminary study of the use of root with Sedline® EEG monitoring for assessment of anesthesia depth in 6 horses. **Applied Sciences** 10:1050, 2020
CROSSREF
10. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). **JAMA** 289:2983-2991, 2003
PUBMED | CROSSREF
11. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. **JAMA** 291:1753-1762, 2004
PUBMED | CROSSREF
12. Flower O, Hellings S. Sedation in traumatic brain injury. **Emerg Med Int** 2012:637171, 2012
PUBMED | CROSSREF
13. Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. **Crit Care** 11:R28, 2007
PUBMED | CROSSREF
14. Goldstein A, Aronow L. The durations of action of thiopental and pentobarbital. **J Pharmacol Exp Ther** 128:1-6, 1960
PUBMED
15. Ha EJ. Pediatric severe traumatic brain injury: Updated management. **J Korean Neurosurg Soc** 65:354-360, 2022
PUBMED | CROSSREF
16. Haddad SH, Arabi YM. Critical care management of severe traumatic brain injury in adults. **Scand J Trauma Resusc Emerg Med** 20:12, 2012
PUBMED | CROSSREF

17. Hausburg MA, Banton KL, Roman PE, Salgado F, Baek P, Waxman MJ, et al. Effects of propofol on ischemia-reperfusion and traumatic brain injury. **J Crit Care** 56:281-287, 2020
PUBMED | CROSSREF
18. Helbok R, Kurtz P, Schmidt MJ, Stuart MR, Fernandez L, Connolly SE, et al. Effects of the neurological wake-up test on clinical examination, intracranial pressure, brain metabolism and brain tissue oxygenation in severely brain-injured patients. **Crit Care** 16:R226, 2012
PUBMED | CROSSREF
19. Henshall DC, Simon RP. Epilepsy and apoptosis pathways. **J Cereb Blood Flow Metab** 25:1557-1572, 2005
PUBMED | CROSSREF
20. Inouye SK. Delirium in older persons. **N Engl J Med** 354:1157-1165, 2006
PUBMED | CROSSREF
21. Jeevaratnam DR, Menon DK. Survey of intensive care of severely head injured patients in the United Kingdom. **BMJ** 312:944-947, 1996
PUBMED | CROSSREF
22. Johnston AJ, Steiner LA, Chatfield DA, Coleman MR, Coles JP, Al-Rawi PG, et al. Effects of propofol on cerebral oxygenation and metabolism after head injury. **Br J Anaesth** 91:781-786, 2003
PUBMED | CROSSREF
23. Kajiwara S, Hasegawa Y, Negoto T, Orito K, Kawano T, Yoshitomi M, et al. Efficacy of a novel prophylactic barbiturate therapy for severe traumatic brain injuries: Step-down infusion of a barbiturate with normothermia. **Neurol Med Chir (Tokyo)** 61:528-535, 2021
PUBMED | CROSSREF
24. Khatri N, Thakur M, Pareek V, Kumar S, Sharma S, Datusalia AK. Oxidative stress: major threat in traumatic brain injury. **CNS Neurol Disord Drug Targets** 17:689-695, 2018
PUBMED | CROSSREF
25. Kim YI, Park SW, Nam TK, Park YS, Min BK, Hwang SN. The effect of barbiturate coma therapy for the patients with severe intracranial hypertension: a 10-year experience. **J Korean Neurosurg Soc** 44:141-145, 2008
PUBMED | CROSSREF
26. Krajčová A, Waldauf P, Anděl M, Duška F. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. **Crit Care** 19:398, 2015
PUBMED | CROSSREF
27. Lee MW, Deppe SA, Sipperly ME, Barrette RR, Thompson DR. The efficacy of barbiturate coma in the management of uncontrolled intracranial hypertension following neurosurgical trauma. **J Neurotrauma** 11:325-331, 1994
PUBMED | CROSSREF
28. Mahmood S, El-Menyar A, Shabana A, Mahmood I, Asim M, Abdelrahman H, et al. Bispectral index as a predictor of unsalvageable traumatic brain injury. **Brain Inj** 31:1382-1386, 2017
PUBMED | CROSSREF
29. Mahmoud L, Zullo AR, Thompson BB, Wendell LC. Outcomes of protocolised analgesia and sedation in a neurocritical care unit. **Brain Inj** 32:941-947, 2018
PUBMED | CROSSREF
30. Matta B, Menon D. Severe head injury in the United Kingdom and Ireland: a survey of practice and implications for management. **Crit Care Med** 24:1743-1748, 1996
PUBMED | CROSSREF
31. Messeter K, Nordström CH, Sundbärg G, Algotsson L, Ryding E. Cerebral hemodynamics in patients with acute severe head trauma. **J Neurosurg** 64:231-237, 1986
PUBMED | CROSSREF
32. Meyfroidt G, Smith M. Focus on delirium, sedation and neuro critical care 2019: towards a more brain-friendly environment? **Intensive Care Med** 45:1292-1294, 2019
PUBMED | CROSSREF
33. Mirski MA, Muffelman B, Ulatowski JA, Hanley DF. Sedation for the critically ill neurologic patient. **Crit Care Med** 23:2038-2053, 1995
PUBMED | CROSSREF
34. Murri L, Arrigo A, Bonuccelli U, Rossi G, Parenti G. Phenobarbital in the prophylaxis of late posttraumatic seizures. **Ital J Neurol Sci** 13:755-760, 1992
PUBMED | CROSSREF
35. Nordström CH, Messeter K, Sundbärg G, Schalén W, Werner M, Ryding E. Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. **J Neurosurg** 68:424-431, 1988
PUBMED | CROSSREF

36. Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, et al. Optimizing sedation in patients with acute brain injury. **Crit Care** 20:128, 2016
PUBMED | CROSSREF

37. Opdenakker O, Vanstraelen A, De Sloovere V, Meyfroidt G. Sedatives in neurocritical care: an update on pharmacological agents and modes of sedation. **Curr Opin Crit Care** 25:97-104, 2019
PUBMED | CROSSREF

38. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. **Curr Opin Anaesthesiol** 21:544-551, 2008
PUBMED | CROSSREF

39. Paul M, Bougouin W, Dumas F, Geri G, Champigneulle B, Guillemet L, et al. Comparison of two sedation regimens during targeted temperature management after cardiac arrest. **Resuscitation** 128:204-210, 2018
PUBMED | CROSSREF

40. Pérez-Bárcena J, Llompart-Pou JA, Homar J, Abadal JM, Raurich JM, Frontera G, et al. Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial. **Crit Care** 12:R112, 2008
PUBMED | CROSSREF

41. Pérez GA, Pérez JA, Álvarez ST, Morales JA, Fragoso AM. Modelling the PSI response in general anesthesia. **J Clin Monit Comput** 35:1015-1025, 2021
PUBMED | CROSSREF

42. Rai S, Drislane FW. Treatment of refractory and super-refractory status epilepticus. **Neurotherapeutics** 15:697-712, 2018
PUBMED | CROSSREF

43. Rey A, Rossetti AO, Miroz JP, Eckert P, Oddo M. Late awakening in survivors of postanoxic coma: early neurophysiologic predictors and association with ICU and long-term neurologic recovery. **Crit Care Med** 47:85-92, 2019
PUBMED | CROSSREF

44. Riker RR, Fraser GL, Wilkins ML. Comparing the bispectral index and suppression ratio with burst suppression of the electroencephalogram during pentobarbital infusions in adult intensive care patients. **Pharmacotherapy** 23:1087-1093, 2003
PUBMED | CROSSREF

45. Rozendaal FW, Spronk PE, Snellen FF, Schoen A, van Zanten AR, Foudraine NA, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. **Intensive Care Med** 35:291-298, 2009
PUBMED | CROSSREF

46. Stover JF, Lenzlinger PM, Stocker R, Morganti-Kossmann MC, Imhof HG, Trentz O, et al. Thiopental in CSF and serum correlates with prolonged loss of cortical activity. **Eur Neurol** 39:223-228, 1998
PUBMED | CROSSREF

47. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. **N Engl J Med** 323:497-502, 1990
PUBMED | CROSSREF

48. Tobias JD. Bispectral index monitoring documents burst suppression during pentobarbital coma. **J Intensive Care Med** 23:258-262, 2008
PUBMED | CROSSREF

49. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. **Anesth Analg** 71:49-54, 1990
PUBMED | CROSSREF

50. Wat R, Mammi M, Paredes J, Haines J, Alasmari M, Liew A, et al. The effectiveness of antiepileptic medications as prophylaxis of early seizure in patients with traumatic brain injury compared with placebo or no treatment: a systematic review and meta-analysis. **World Neurosurg** 122:433-440, 2019
PUBMED | CROSSREF

51. Winer JW, Rosenwasser RH, Jimenez F. Electroencephalographic activity and serum and cerebrospinal fluid pentobarbital levels in determining the therapeutic end point during barbiturate coma. **Neurosurgery** 29:739-741, 1991
PUBMED | CROSSREF

52. Yerram S, Katyal N, Premkumar K, Nattanmai P, Newey CR. Seizure prophylaxis in the neuroscience intensive care unit. **J Intensive Care** 6:17, 2018
PUBMED | CROSSREF

https://doi.org/10.13004/kjnt.2023.19.e19

53. Zaal IJ, Devlin JW, Hazelbag M, Klein Klouwenberg PM, van der Kooi AW, Ong DS, et al. Benzodiazepine-associated delirium in critically ill adults. **Intensive Care Med** 41:2130-2137, 2015
PUBMED | CROSSREF

54. Zeitzer JM, Friedman L, O'Hara R. Insomnia in the context of traumatic brain injury. **J Rehabil Res Dev** 46:827-836, 2009
PUBMED | CROSSREF

https://doi.org/10.13004/kjnt.2023.19.e19