Chapter 15. Analgesics, sedatives, and neuromuscular blockade

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low, from poor-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III*

Etomidate may be considered to control severe intracranial hypertension; however, the risks resulting from adrenal suppression must be considered.

Thiopental may be considered to control intracranial hypertension.

*In the absence of outcome data, the specific indications, choice and dosing of analgesics, sedatives, and neuromuscular-blocking agents used in the management of infants and children with severe traumatic brain injury (TBI) should be left to the treating physician.

***As stated by the Food and Drug Administration, continuous infusion of propofol for either sedation or the management of refractory intracranial hypertension in infants and children with severe TBI is not recommended.**

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Analgesics, sedatives, and neuromuscular-blocking agents are commonly used in the management severe pediatric TBI. Use of these agents can be divided into two major categories: 1) for emergency intubation; and 2) for management including control of elevated intracranial pressure (ICP) in the intensive care unit (ICU). This chapter evaluates these agents during ICU treatment.

Analgesics and sedatives are believed to favorably treat a number of important pathophysiological derangements in severe TBI. They can facilitate necessary general aspects of patient care such as the ability to maintain the airway, vascular catheters, and other monitors. They can also facilitate patient transport for diagnostic procedures and mechanical ventilatory support. Other proposed benefits of sedatives after severe TBI include anticonvulsant and antiemetic actions, the prevention of shivering, and attenuating the long-term psychological trauma of pain and stress. Analgesics and sedatives also are believed to be useful by mitigating aspects of secondary damage. Pain and stress markedly increase cerebral metabolic demands and can pathologically increase cerebral blood volume and raise ICP. Studies in experimental models showed that a two- to threefold increase in cerebral metabolic rate for oxygen accompanies painful stimuli (1, 2). Noxious stimuli such as suctioning can also increase ICP (3–6). Painful and noxious stimuli and stress can also contribute to increases in sympathetic tone with hypertension and bleeding from operative sites (7). However, analgesic or sedative-induced reductions in arterial blood pressure can lead to cerebral ischemia as well as vasodilation and can exacerbate increases in cerebral blood volume and ICP. In the absence of advanced neuromonitoring, care must be taken to avoid this complication.

The ideal sedative for patients with severe TBI has been described as one that is rapid in onset and offset, easily titrated to effect, has well-defined metabolism (preferably independent of end-organ function), neither accumulates nor has active metabolites, exhibits anticonvulsant actions, has no adverse cardiovascular or immune actions, and lacks drug–drug interactions while preserving the neurologic examination (8).

Neuromuscular-blocking agents have been suggested to reduce ICP by a variety of mechanisms including a reduction in airway and intrathoracic pressure with facilitation of cerebral venous outflow and by prevention of shivering, posturing, or breathing against the ventilator (9). Reduction in metabolic demands by elimination of skeletal muscle contraction has also been suggested to represent a benefit. Risks of neuromuscular blockade include the potential devastating effect of hypoxemia secondary to inadvertent extubation, risks of masking seizures, increased incidence of nosocomial pneumonia (shown in adults with severe TBI) (9), cardiovascular side effects, immobilization stress (if neuromuscular blockade is used without adequate sedation/analgesia), and increased ICU length of stay (9, 10). Myopathy is most commonly seen with the combined use of nondepolarizing agents and corticosteroids. Incidence of this complication varies between 1% and over 30% of cases (5, 11, 12). Monitoring of the depth of neuromuscular blockade can shorten duration of its use in the ICU (13).

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 46 potentially relevant studies, two were included as evidence for this topic.

V. SCIENTIFIC FOUNDATION

The recommendations on the use of analgesics, sedatives, and neuromuscular-blocking agents in this chapter are for patients with a secure airway who are receiving mechanical ventilatory support yielding the desired arterial blood gas values and who have stable systemic hemodynamics and intravascular volume status.

Two class III studies of the use of analgesics or sedatives met inclusion criteria for this topic and provide evidence to support the recommendations: one study about etomidate and one about thiopental. These studies only addressed ICP as the outcome (14, 15). No study addressed the most commonly used analgesics and sedatives (narcotics and benzodiazepines).

Etomidate

A study by Bramwell et al (14) carried out a prospective unblinded class III study of the effect of a single dose of

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Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
New studies			
Bramwell et al, 2006 (14)	Design: prospective case series N = 8 Age: <15 yrs Protocol: single IV dose of etomidate (0.3 mg/kg) Purpose: determine if etomidate reduces ICP in the setting of intracranial hypertension (ICP >20 mm Hg) Outcome: ICP	Class III Poor quality: no control for confounders; very small sample size	Etomidate administration resulted in a decrease in ICP vs. baseline ($p < .05$) without change in mean arterial pressure, thereby increasing cerebral perfusion pressure at each 5-min interval; at 6 hrs after etomidate administration, adrenocorticotropic hormone stimulation tests showed adrenal suppression in 4 of the 8 patients; however, no patient required treatment with steroids
de Bray et al, 1993 (15)	Design: prospective case series N = 10 TBI and 10 orthopedic controls Age: 4–14 yrs Protocol: IV administration of thiopental and Doppler assessment of middle cerebral artery flow velocity Purpose: assess the effect of thiopental (5 mg/kg, IV) on ICP and middle cerebral artery flow velocity Outcome: middle cerebral artery flow velocity blood velocity, measured at the time of greatest decrease of mean arterial pressure after thiopental administration, compared with baseline	Class III Poor quality: no control for confounders; unclear if selection was unbiased; unclear if missing data	Thiopental reduced mean ICP, measured in 6 of the 10 patients with TBI, by 48% ($p < .01$), with no significant correlation with middle cerebral artery flow velocity; thiopental also reduced middle cerebral artery flow velocity (systolic velocities $-15\% \pm 6.9\%$, $p < .01$) and diastolic velocities ($-21\% \pm 6.5\%$, $p < .01$) in cases, not controls; reduction in middle cerebral artery flow velocity occurred in 90% cases compared with 10% controls; mean ICP, measured in 6 of the 10 patients with TBI, was reduced by 48% ($p < .01$) with no significant correlation with middle cerebral artery flow velocity

IV, intravenous; ICP, intracranial pressure; TBI, traumatic brain injury.

etomidate (0.3 mg/kg, intravenously) on ICP >20 mm Hg in eight children with severe TBI. Etomidate reduced ICP vs. baseline in each 5-min interval during the 30-min study period. The patients in this study had severe intracranial hypertension and etomidate reduced ICP from 32.8 ± 6.6 mm Hg to 21.2 ± 5.2 mm Hg. An increase in cerebral perfusion pressure was also seen that was significant for the initial 25 mins after etomidate administration. Every patient in the study exhibited a reduction in ICP with treatment. No data were presented on cortisol levels in these patients. However, in the discussion section of the manuscript, the authors indicated that at 6 hrs after etomidate administration, adrenocorticotropic hormone stimulation tests were performed on each patient; four of the eight showed adrenal suppression. It is unclear if this degree of adrenal suppression is different from that normally observed in pediatric TBI (16). No patient showed clinical signs of adrenal insufficiency such as electrolyte disturbances or blood pressure lability, and no patient received steroid therapy.

The availability of other sedatives and analgesics that do not suppress adrenal function, small sample size and single-dose administration in the study discussed previously, and limited safety profile in pediatric TBI limit the ability to endorse the general use of etomidate as a sedative other than as an option for single-dose administration in the setting of raised ICP.

Barbiturates

Barbiturates can be given as a sedative at doses lower than those required to induce or maintain barbiturate coma. No report specifically addressed their use in that capacity in pediatric TBI. One report did, however, address the effects of barbiturate administration outside of the setting of refractory raised ICP. A study by de Bray et al (15) was a prospective study of the effect of a single dose of thiopental (5 mg/kg, intravenously) on middle cerebral artery flow velocity in ten children with severe TBI and compared the findings with those seen with thiopental administration in ten children under general anesthesia for orthopedic procedures. In this small study, effects on ICP were assessed in only six of the ten children with severe TBI. In those six, thiopental reduced ICP by 48%. Flow velocity was reduced by approximately 15% to 21% in the pediatric patients with TBI. Baseline ICP was 16.5 mm Hg. Cerebral perfusion pressure was not significantly changed. At the class III level, this study supports the ability of thiopental, administered as a single dose, to reduce ICP, even when only moderately increased. The effects on flow velocity are also consistent with the reduction in cerebral blood volume that would be expected to mediate the reduction in ICP produced by thiopental. No study was identified, however, that specifically addressed barbiturate use as a sedative on any other outcome parameter.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

In the most recent adult guidelines, a chapter on "Anesthetics, Analgesics, and Sedatives" identified a class II study to recommend continuous infusion of propofol as the agent of choice.

Only case reports or mixed adult and pediatric case series have been published supporting propofol use in pediatric TBI

(17, 18). However, a number of reports (in cases not restricted to TBI) suggest that continuous infusion of propofol is associated with an unexplained increase in mortality risk in critically ill children. A syndrome of lethal metabolic acidosis ("propofol syndrome") can occur (19–24). In light of these risks, and with alternative therapies available, continuous infusion of propofol for either sedation or management of refractory intracranial hypertension in severe pediatric TBI is not recommended. The Center for Drug Evaluation and Research Web site of the Food and Drug Administration (25) states, "Propofol is not indicated for pediatric ICU sedation as safety has not been established." Based on the Food and Drug Administration recommendations against the continuous infusion of propofol for sedation in pediatric critical care medicine, the recommendation from the adult guidelines cannot be translated to pediatric TBI management and represents an important discontinuity between pediatric and adult TBI management.

Neuromuscular-blocking agents were not addressed in the "Anesthetics, Analgesics, and Sedatives" chapter of the most recent adult guidelines. In the 2000 adult guidelines (26), the initial management section cited a study that examined 514 entries in the Traumatic Coma Data Bank and reported no beneficial effects of neuromuscular blockade and an increased incidence of nosocomial pneumonia and prolonged ICU stay associated with prophylactic neuromuscular blockade (9). It was suggested that use of neuromuscular-blocking agents be reserved for specific indications (intracranial hypertension, transport).

B. Information Not Included as Evidence

Ketamine exhibits neuroprotective effects in experimental models of TBI; however, concerns over its vasodilatory effects and their impact on ICP have long limited its consideration as a sedative in TBI. Recently, a study by Bar-Joseph et al (27) was carried out, which was a prospective study in 30 children with raised ICP, 24 with nonpenetrating TBI. A single dose of ketamine (1–1.5 mg/kg, intravenously) was evaluated for its ability to either 1) prevent further increases in ICP during a stressful procedure (i.e., suctioning); or 2) treat refractory intracranial hypertension. Ketamine reduced ICP in both settings. These patients had severe intracranial hypertension with an overall mean ICP of 25.8 mm Hg. The study did not meet inclusion criteria for these guidelines for two reasons. First, it fell just below the cutoff of 85% of TBI cases, and second, Glasgow Coma Scale score was not provided–although it is likely that the children had severe TBI given the ICP data.

Regarding the use of etomidate in critical care, including severe TBI and multiple trauma victims (28–31), there are general concerns over adrenal suppression. As stated earlier, the availability of other sedatives and analgesics that do not suppress adrenal function, along with the small sample size and single-dose administration in the single study in the evidence table (Table 1) and limited safety profile in pediatric TBI, limit the ability to endorse the general use of etomidate as a sedative other than as an option for single-dose administration in the setting of raised ICP.

VII. SUMMARY

Two studies were identified that met inclusion criteria, rendering reserved class III recommendations that 1) etomidate may be considered to decrease intracranial hypertension, although the risks resulting from adrenal suppression must be considered; and 2) thiopental, given as a single dose, may be considered to control intracranial hypertension.

Despite the common use of analgesics and sedatives in TBI management, there have been few studies of these drugs focused on pediatric patients with severe TBI, and studies meeting inclusion criteria for the most commonly used agents were lacking. Similarly, no studies were identified meeting inclusion criteria that addressed the use of neuromuscular blockade in pediatric patients with severe TBI. Until experimental comparisons among these agents are carried out, the choice and dosing of analgesics, sedatives, and neuromuscular-blocking agents used should be left to the treating physician. Based on recommendations of the Food and Drug Administration, continuous infusion of propofol is not recommended in the treatment of pediatric TBI.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Studies are needed comparing the various sedatives and analgesics in pediatric patients with severe TBI, examining sedative and analgesic efficacy, effects on ICP, other surrogate markers, and functional outcome.
- Studies are needed to assess the toxicities, including hypotension, adrenal suppression, effects on long-term cognitive outcomes, and other adverse effects.
- Studies are needed on dosing, duration, and interaction effects with other concurrent therapies.
- Optimal sedation after severe TBI may differ between infants and older children and requires investigation. Specifically, given concerns over the effects of various anesthetics and sedatives on neuronal death in the developing brain (32, 33), studies of various analgesic and sedative regimens in infants with TBI are needed, including infants who are victims of abusive head trauma.
- The specific role of neuromuscular-blocking agents in infants and children with severe TBI needs to be defined.

REFERENCES

1. Nilsson B, Rehncrona S, Siesjo BK: Coupling of cerebral metabolism and blood flow in epileptic seizures, hypoxia and hypoglycaemia. *Ciba Found Symp* 1978; 56:199–218
2. Rehncrona S, Siesjo BK: Metabolic and physiologic changes in acute brain failure. *In*: Brain Failure and Resuscitation. Grenvik A, Safar P (Eds). New York, NY, Churchill Livingstone, 1981, pp 11–33
3. Fortune JB, Feustel PJ, Weigle CG, et al: Continuous measurement of jugular venous oxygen saturation in response to transient elevations of blood pressure in head-injured patients. *J Neurosurg* 1994; 80:461–468
4. Kerr ME, Weber BB, Sereika SM, et al: Effect of endotracheal suctioning on cerebral oxygenation in traumatic brain-injured patients. *Crit Care Med* 1999; 27:2776–2781
5. Raju TN, Vidyasagar D, Torres C, et al: Intracranial pressure during intubation and anesthesia in infants. *J Pediatr* 1980; 96:860–862
6. White PF, Schlobohm RM, Pitts LH, et al: A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. *Anesthesiology* 1982; 57:242–244
7. Todres ID: Post anesthesia recovery in the pediatric intensive care unit. *In*: Pediatric Critical Care. BP, F, JJ, Z (Eds). St. Louis, MO, Mosby, 1998, pp 1391–1398
8. Prielipp RC, Coursin DB: Sedative and neuromuscular blocking drug use in critically ill patients with head injuries. *New Horiz* 1995; 3:456–468
9. Hsiang JK, Chesnut RM, Crisp CB, et al: Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? *Crit Care Med* 1994; 22:1471–1476
10. Durbin CG Jr: Neuromuscular blocking

agents and sedative drugs. Clinical uses and toxic effects in the critical care unit. *Crit Care Clin* 1991; 7:489–506
11. Douglass JA, Tuxen DV, Horne M, et al: Myopathy in severe asthma. *Am Rev Respir Dis* 1992; 146:517–519
12. Rudis MI, Guslits BJ, Peterson EL, et al: Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. *Crit Care Med* 1996; 24:1749–1756
13. Rudis MI, Sikora CA, Angus E, et al: A prospective, randomized, controlled evaluation of peripheral nerve stimulation versus standard clinical dosing of neuromuscular blocking agents in critically ill patients. *Crit Care Med* 1997; 25:575–583
14. Bramwell KJ, Haizlip J, Pribble C, et al: The effect of etomidate on intracranial pressure and systemic blood pressure in pediatric patients with severe traumatic brain injury. *Pediatr Emerg Care* 2006; 22:90–93
15. de Bray JM, Granry JC, Monrigal JP, et al: Effects of thiopental on middle cerebral artery blood velocities: A transcranial Doppler study in children. *Childs Nerv Syst* 1993; 9:220–223
16. Acerini CL, Tasker RC: Endocrine sequelae of traumatic brain injury in childhood. *Horm Res* 2007; 68(Suppl 5):14–17
17. Farling PA, Johnston JR, Coppel DL: Propofol infusion for sedation of patients with head injury in intensive care. A preliminary report. *Anaesthesia* 1989; 44:222–226
18. Spitzfaden AC, Jimenez DF, Tobias JD: Propofol for sedation and control of intracranial pressure in children. *Pediatr Neurosurg* 1999; 31:194–200
19. Bray RJ: Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; 8:491–499
20. Canivet JL, Gustad K, Leclercq P, et al: Massive ketonuria during sedation with propofol in a 12 year old girl with severe head trauma. *Acta Anaesth Belg* 1994; 45:19–22
21. Cray SH, Robinson BH, Cox PN: Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med* 1998; 26:2087–2092
22. Fong JJ, Sylvia L, Ruthazer R, et al: Predictors of mortality in patients with suspected propofol infusion syndrome. *Crit Care Med* 2008; 36:2281–2287
23. Hanna JP, Ramundo ML: Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology* 1998; 50:301–303
24. Parke TJ, Stevens JE, Rice AS, et al: Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. *BMJ* 1992; 305:613–616
25. The Food and Drug Administration: Center for Drug Evaluation and Research. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172351.htm; http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173766.pdf. Accessed February 17, 2010
26. The Brain Trauma Foundation; The American Association of Neurological Surgeons: The Joint Section on Neurotrauma and Critical Care. Initial management. *J Neurotrauma* 2000; 17:463–469
27. Bar-Joseph G, Guilburd Y, Tamir A, et al: Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009; 4:40–46
28. Cohan P, Wang C, McArthur DL, et al: Acute secondary adrenal insufficiency after traumatic brain injury: A prospective study. *Crit Care Med* 2005; 33:2358–2366
29. Cotton BA, Guillamondegui OD, Fleming SB, et al: Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. *Arch Surg* 2008; 143:62–67; discussion 67
30. Hildreth AN, Mejia VA, Maxwell RA, et al: Adrenal suppression following a single dose of etomidate for rapid sequence induction: A prospective randomized study. *J Trauma* 2008; 65:573–579
31. Warner KJ, Cuschieri J, Jurkovich GJ, et al: Single-dose etomidate for rapid sequence intubation may impact outcome after severe injury. *J Trauma* 2009; 67:45–50
32. Bittigau P, Sifringer M, Pohl D, et al: Apoptotic neurodegeneration following trauma is markedly enhanced in the immature brain. *Ann Neurol* 1999; 45:724–735
33. Ikonomidou C, Bittigau P, Koch C, et al: Neurotransmitters and apoptosis in the developing brain. *Biochem Pharmacol* 2001; 62:401–405