

Chapter 9. Use of sedation and neuromuscular blockade in the treatment of severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.*

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.*

C. Options. In the absence of outcome data, the choice and dosing of sedatives, analgesics, 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. However, the effect of individual sedatives and analgesics on intracranial pressure (ICP) in infants and children with severe TBI can be variable and unpredictable.

D. Indications from Adult Guidelines. The guidelines on the management of adults with severe TBI (1) did not include a specific chapter on the use of sedation, analgesia, or neuromuscular blockade.

In the chapter on initial management (2), it was stated that neuromuscular blocking agents can facilitate mechanical ventilation and management of raised ICP, but their use should be reserved for specific indications. The depth and duration of neuromuscular blockade should be monitored and optimized, respectively.

II. OVERVIEW

Sedatives, analgesics, and neuromuscular blocking agents are commonly used in the management of infants and children with severe TBI. Use of these agents can be divided into two major categories: a) for emergency intubation, and b) for management including control of ICP in the intensive care unit (ICU). The use of

*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 traumatic brain injury is not recommended.

sedatives, analgesics, and neuromuscular blocking agents for emergency intubation is addressed in chapter 3. This section evaluates use of sedation, analgesia, and neuromuscular blockade during ICU treatment.

Despite their common use in the management of severe TBI in infants and children, sedatives, analgesics, and neuromuscular blocking agents have been subjected to very limited clinical investigation. Most of the medical literature on these agents in pediatric TBI consists of either descriptions of small numbers of children included in adult studies (but not fully described) or case reports—often describing an unanticipated response to administration of a given agent. The lack of high-quality pediatric studies severely limits any conclusions that can be made.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 40 potentially relevant studies, one was used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

A. Sedation and Analgesia. The recommendations on the use of sedatives, analgesics, 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. Sedatives and analgesics are believed to favorably treat a number of important pathophysiologic 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. Sedatives and analgesics also can facilitate patient

transport for diagnostic procedures. Sedatives and analgesics 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 three-fold increase in cerebral metabolic rate for oxygen accompanies painful or stressful stimuli (3, 4). Noxious stimuli such as suctioning also can increase ICP (5–8). Painful and noxious stimuli and stress also can contribute to increases in sympathetic tone, with hypertension, and bleeding from operative sites (9). However, sedative-induced reductions in arterial blood pressure can lead to cerebral vasodilation and exacerbate increases in cerebral blood volume and ICP. In the absence of advanced monitoring, care must be taken to avoid this complication.

Sedatives and analgesics are used to treat painful and noxious stimuli. They also facilitate mechanical ventilatory support. Other proposed benefits of sedatives after severe TBI include anticonvulsant and anti-emetic actions, the prevention of shivering, and mitigation of the long-term psychological trauma of pain and stress. Prielipp and Coursin (10) described the ideal sedative for patients with severe TBI as one that is rapid in onset and offset, is 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.

Eight studies were identified that addressed the use of sedatives and/or analgesics in severe pediatric TBI. However, none of these reports reached the level of class III data. All either were studies in adults that included a small unstratified

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Vernon and Witte (33), 2000	Prospective, unblinded crossover study of the effect of neuromuscular blockade on oxygen consumption in 20 mechanically ventilated children, six of whom had severe TBI.	II ^c	Neuromuscular blockade reduced oxygen consumption and energy expenditure $8.7 \pm 1.7\%$ and $10.3 \pm 1.8\%$, respectively. Although the effect was significant, the magnitude was modest.

TBI, traumatic brain injury.

^cClass II evidence only for the effect of neuromuscular blockade on oxygen consumption—not on long-term outcome.

number of children or were case reports. The sedatives and analgesics in these studies included narcotics, benzodiazepines, ketamine, and propofol.

Tobias (11) reported that bolus fentanyl ($5 \mu\text{g}/\text{kg}$ body weight) produced a spike in ICP in an 11-yr-old child with severe TBI. ICP responded to barbiturate and mannitol administration. Remarkably, this is the only identified report on either fentanyl or morphine use in the management of ICP in pediatric TBI. Albanese et al. (12) studied the effect of sufentanil ($1 \mu\text{g}/\text{kg}$ intravenous bolus plus infusion) on ICP in ten comatose patients with severe TBI, including three adolescents. Sufentanil increased ICP 9 ± 7 mm Hg and decreased cerebral perfusion pressure (CPP) 38% after administration. Infusion of the ultra-short-acting narcotic remifentanyl controlled refractory ICP in a 16-yr-old child with severe TBI, when hypotension limited propofol use (13).

Cotev and Shalit (14) studied the effect of diazepam in eight patients with severe TBI, including one adolescent. An $\sim 25\%$ reduction in cerebral metabolic rate for oxygen and cerebral blood flow was seen without an effect on blood pressure. Studies of other commonly used benzodiazepines (midazolam, lorazepam) in pediatric TBI are lacking. Albanese et al. (15) studied the effect of ketamine ($1.5, 3,$ and $5 \text{ mg}/\text{kg}$ intravenous boluses) on ICP and electroencephalogram in eight patients (including three teenagers) with severe TBI. Surprisingly, bolus doses of ketamine, a sedative agent that has been contraindicated for use in the setting of increased ICP, was associated with a 2–5 mm Hg reduction in ICP.

Spitzfaden et al. (16) reported successful treatment of refractory intracranial hypertension in a 7-yr-old with TBI using continuous infusion of propofol ($3\text{--}5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ for 4 days). Similarly, Farling et al. (17) reported a study on the effect of propofol (intravenous infusion of

$1.04\text{--}4.97 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) in ten comatose patients (including two teenagers) with severe TBI. Propofol infusion (for 24 hrs) produced adequate sedation and no major changes in ICP or CPP. However, a number of reports (in cases not restricted to TBI) suggest that administration of propofol by continuous infusion is associated with an unexplained increase in mortality risk. A syndrome of lethal metabolic acidosis can occur (18–22). “Propofol syndrome” also has been reported in an adult with severe TBI (23). 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 (24) of the FDA states, “Propofol is not indicated for pediatric ICU sedation as safety has not been established.”

Although there is one report of sedation with infusion of etomidate in TBI that included children (25), lack of age stratification made it impossible to define its effect in the pediatric subgroup. No articles were located that evaluated the use of lidocaine to blunt the response to airway stimulation in children with severe TBI. Finally, barbiturates can be given as sedatives by using doses lower than those required to induce barbiturate coma. The use of high-dose barbiturates in the management of infants and children with severe TBI will be addressed in Chapter 13.

B. Neuromuscular Blockade. Neuro-muscular 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 (26). Reduction in metabolic demands by elimination of skeletal muscle contraction also

has been suggested to represent a beneficial effect of neuromuscular blockade.

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) (26), cardiovascular side effects, immobilization stress (if neuromuscular blockade is used without adequate sedation and analgesia), and increased ICU length of stay (26, 27). Myopathy is most commonly seen with the combined use of nondepolarizing agents and corticosteroids. Incidence of this complication varies greatly between studies and ranges between 1% and $>30\%$ of cases (28–30). Monitoring of the depth of neuromuscular blockade can shorten duration of neuromuscular blockade in the ICU (31).

Two pediatric studies of neuromuscular blocking agents, which were not restricted to children with TBI, suggest that these agents are more commonly used in the management of critically ill infants and children than in adults—as much as five times more common (28, 32). However, only two studies were identified that addressed the use of neuromuscular blocking agents in the setting of severe pediatric TBI (33, 34). One of these reports reached the level of class II data for the effect of neuromuscular blocking agents on systemic oxygen consumption. Vernon et al. (33) performed a prospective, unblinded crossover study of the effect of neuromuscular blockade with vecuronium or pancuronium on total body oxygen consumption in 20 mechanically ventilated children, six of whom had severe TBI. Neuromuscular blockade reduced oxygen consumption and energy expenditure $8.7 \pm 1.7\%$ and $10.3 \pm 1.8\%$, respectively. The authors concluded that although neuromuscular blockade reduces oxygen consumption, the degree of reduction is small. No study of the efficacy of specific therapeutic ap-

Based on recommendations of the Food and Drug Administration, continuous infusion of propofol is not recommended in the treatment of pediatric traumatic brain injury.

proaches to neuromuscular blockade in the treatment of pediatric TBI was identified. Finally, in a study of eight patients (including two adolescents), continuous infusion of doxacurium provided stable neuromuscular blockade without altering ICP or CPP and was less expensive than other commonly used agents (34).

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

In the chapter on initial management (2) in the adult guidelines, it was stated that approaches to sedation and neuromuscular blockade vary widely. There have been no studies on the influence of sedation on outcome from severe TBI; therefore, the decisions on the use of sedation and the choice of sedative agents were left up to the treating physician. Adult guidelines also were not written for the use of neuromuscular blocking agents. However, the initial management section cited one class II study by Hsiang et al. (26) that examined 514 entries in the Traumatic Coma Data Bank and reported an increased incidence of nosocomial pneumonia and prolonged ICU stay associated with early prophylactic use of neuromuscular blockade. It was suggested that use of neuromuscular blocking agents be reserved for specific indications (intracranial hypertension, transport).

V. SUMMARY

There were no studies with sedatives or analgesics providing acceptable evidence for the present report. There was only one study of the use of neuromuscular blockade that qualified as class II,

and that involved the effect of neuromuscular blockade on oxygen consumption only. Until experimental comparisons among specific regimens of these sedative, analgesic, and neuromuscular blocking agents are carried out, the choice and dosing of sedatives and analgesic agents used in the management of infants and children with severe TBI should be left to the treating physician.

Based on recommendations of the FDA, continuous infusion of propofol is not recommended in the treatment of pediatric TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Additional study is needed comparing the various sedatives and analgesics in pediatric patients with severe TBI. Assessments are needed of optimal agents, dosing, duration, and interaction effects with other concurrent therapies. Study of the effect of various sedation strategies on the development and therapeutic intensity level of intracranial hypertension also is needed. Although multiple-center trials assessing the effect of these agents on outcome would be optimal, based on the current dearth of investigation on the use of sedatives and analgesics in pediatric TBI, even case series or small cohort studies would advance the literature. Similarly lacking are studies addressing the important issue of age-related differences and the unique subgroup of infants who are victims of abusive head trauma. The issue of age-related differences may be of particular importance in the area of sedation, since studies in experimental animal models of TBI suggest that some level of synaptic activation is essential to normal development in infancy and that anti-excitotoxic agents may trigger apoptosis in the injured brain (35, 36). Thus, optimal sedation after severe TBI may differ between infants and older children and deserves specific investigation. Finally, the specific role of neuromuscular blocking agents in infants and children with severe TBI also remains to be studied.

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APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 9. Sedation and Neuromuscular Blockade

1. exp craniocerebral trauma/
2. head injur\$.tw.
3. brain injur\$.tw.
4. 1 or 2 or 3
5. brain ischemia/ or “cerebral ischemia”.mp.
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)