VANDERBILT UNIVERSITY
MEDICAL CENTER
DIVISION OF ACUTE CARE SURGERY

Pentobarbital Treatment Guidelines for Severe Traumatic Brain Injury

Rationale: Pentobarbital (PB) and other barbiturates have been shown in human and animal studies to have neuroprotective effects on patients with traumatic brain injury. Pentobarbital reduces cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) and thus, a reduction in intracranial pressure (ICP). This occurs in a dose-dependent fashion.

Current guidelines from the Brain Trauma Foundation report a low-quality body of evidence to support the use of high-dose barbiturates to control elevated ICP refractory to maximum medical & surgical treatment. Therefore, it is recommended as a second-line agent for treatment of refractory intracranial hypertension (RICH). A systematic review published in 2012 reported that in the adult population, though barbiturates reduce ICP, there was no significant evidence that its use is associated with a decrease in death or disability. Several studies identified early responders (i.e., improvement in ICPs within 48h of PB initiation) as having a higher chance of full recovery. There is a small body of evidence in the pediatric population showing use of high-dose barbiturates helped to control ICP and was associated with improved long-term outcomes. Therefore, it continues to be used as a potential salvage therapy for patients with RICH. It is essential to ensure that families understand that this treatment is a salvage therapy for injuries associated with very high morbidity and mortality.

PB Coma Candidate Criteria (must meet ALL the following criteria):

Refractory Intracranial Hypertension (RICH):
- ICP 21-35 for 4 hours
- ICP 36-40 for 1 hour
- ICP >40 for 5 minutes

*ICP elevation in absence of stimulation/agitation

Head of bed maximally elevated

Ventilation and pCO_2 optimized

Max hyperosmolar therapy
*(Na ≥160 mmol/L **AND** serum osmolality ≥ 330 mOsm/kg H_2O)*

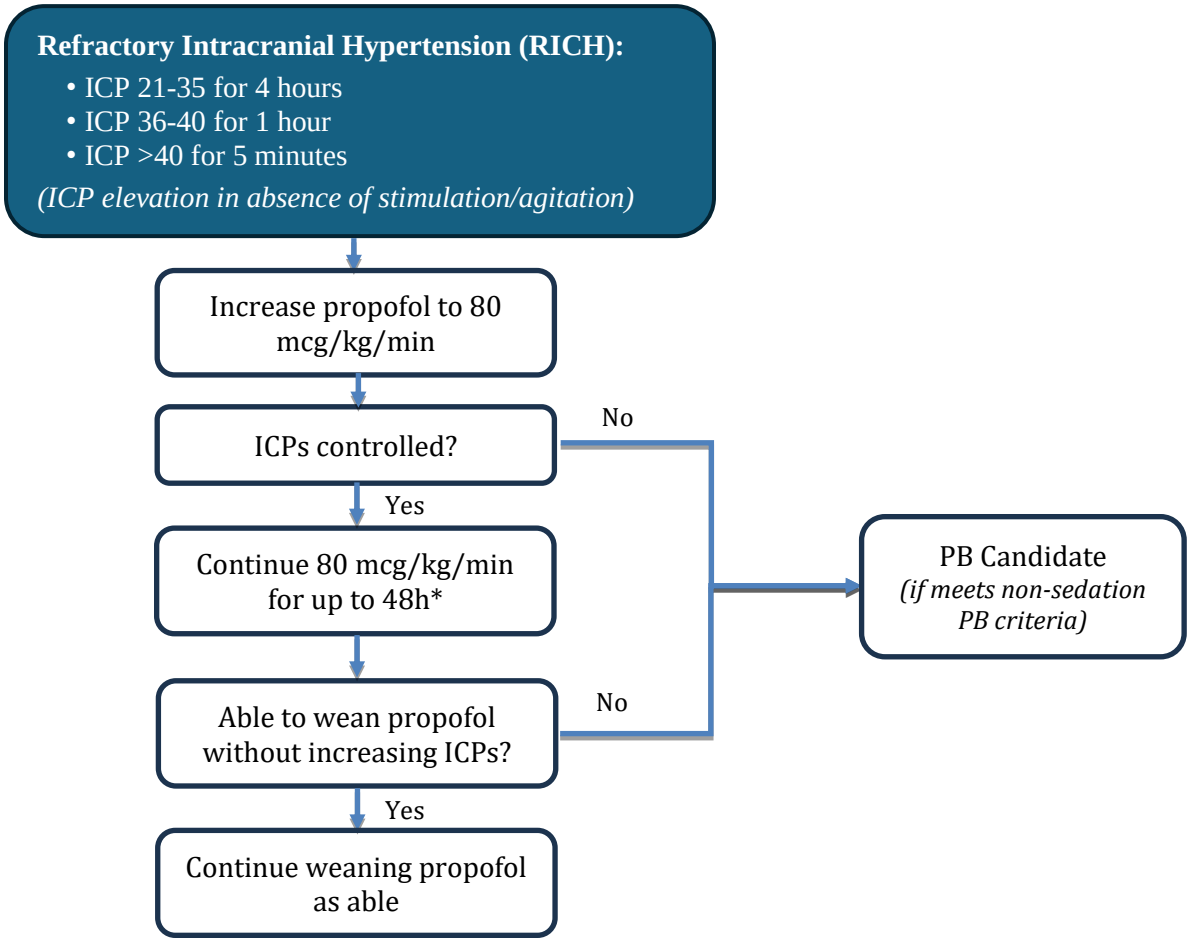
Sedation to RASS -5

Propofol use exhausted
(see next page)

No surgically treatable lesions on repeat CTH **AND** NSGY agrees with PB coma

Palliative care consulted or re-consulted upon initiation of PB coma

Sedation Use Guidance:



***Monitor for Propofol Intolerance:**

- Propofol Infusion Syndrome (PRIS)
  - Severe high anion gap metabolic acidosis
  - Cardiac arrhythmias (i.e. afib, vtach, vfib)
  - Rhabdomyolysis **(monitor CK daily)**
  - Cardiovascular collapse
  - Hyperkalemia
  - AKI
- Propofol-induced Triglyceridemia
  - Triglycerides >500 mg/dL (**monitor triglyceride level daily**)
- Hemodynamic instability
  - High dose pressor requirement to maintain CPP goal

****Transition to midazolam 0-10 mg/hr if propofol intolerance develops**

Pentobarbital Use:

I. **Goal of Pentobarbital Treatment:** ICP controlled <20 for at least 48 hours

II. **Dosing of Pentobarbital:**
   I. Start pentobarbital load: 10 mg/kg intravenous bolus over 60 minutes followed by 5 mg/kg/hr continuous infusion x 3 hours
   II. Decrease PB infusion rate to 1 mg/kg/hr and discontinue propofol infusion after completion of load.
   III. Titrate infusion rate (1-5 mg/kg/hr) to maintain burst suppression goal (2-5 bursts/min).
      i. **<u>Only providers are allowed to interpret EEGs and titrate the pentobarbital infusion.</u>**
   IV. Continue burst suppression for at least 72 hours.
   V. After 72 hours of treatment, if ICPs have been controlled for at least 48 hours, begin weaning pentobarbital.
      i. Reduce the dose by 50% every 12 hours until the infusion rate falls below 0.5 mg/kg/hr, at which point it should be turned off.
      ii. If ICPs become uncontrolled as defined by RICH criteria within the first 12 hours of the infusion being turned off, resume infusion rate which previously achieved goal burst suppression for at least another 48-hour period prior to attempting wean again.
         I. If burst suppression is not achieved at previous rate, modify rate accordingly to achieve appropriate suppression.
         II. Do not re-bolus pentobarbital.

Non-Responder to treatment defined as:

- *Once goal burst suppression is reached*, ICPs persistently uncontrolled at:
  1. 21-35 for 4 hours
  2. 36-40 for 1 hour
  3. >40 for 5 minutes
- Provider team and patient surrogate must be notified that patient is a non-responder as soon as it occurs. Discontinue pentobarbital therapy.

PB-Responder with failure of treatment defined as:

1. Failure of ICPs to normalize after multiple failed weaning attempts
2. Failure of ICPs to return to <20 in 7 days without pentobarbital
3. Brain death/herniation
4. Severe side effects requiring discontinuation of treatment (hypotension, etc.)

Additional Monitoring:

1. Continuous EEG order *Do not delay initiation of pentobarbital load for EEG setup*
2. Continue monitoring & treatment with hyperosmolar therapy if Na becomes <160 mmol/L and/or serum osmolality becomes <330 mOsm/kg H_2O during treatment with PB.
3. Check LFTs prior to initiation of pentobarbital infusion and then every 72 hours during treatment.
4. Continue enteral feeding while patient is receiving pentobarbital. Monitor for intolerance but do not hold unless indicated.

Special Considerations

- **Determination of brain death should be based on cerebral brain flow study only.**
- **For transitioning to comfort care and potential DCD patients, send post-infusion pentobarbital level 72 hours after discontinuation of infusion to allow for adequate drug clearance prior to next phase of care.**
    - *How to order: Pentobarbital will need to be ordered as a MISC RFT, miscellaneous reference test, and the ordering provider will need to specify –"send pentobarbital level to Medtox laboratories" in the order. Otherwise, the test will get sent out to ARUP. Results will come back under the media tab as a scanned laboratory report.*
    - *Nurse reference for proper collection: https://medtox.labcorp.com/tests/701768/pentobarbital-immunoassay-serum-plasma*

Propylene Glycol Toxicity

- Propylene glycol toxicity should be considered in patients with an unexplained anion gap, osmolar gap, elevated lactate, and/or acute renal failure.
    - May consider nephrology consultation for dialysis or consider use of fomepizole (consult toxicology and pharmacy for dosing).

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References

1. Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg* 1988;69: 15-23.
2. Kochanek, P., Carney, N., Adelson, P., Ashwal, S., et al. Chapter 11, Barbiturates. *Pediatric Critical Care Medicine.* 2012; 13: S49-S52.
3. Carney, N., Totten, A., O'Reilly, C., Ullman, J., et al. Guidelines for the management of severe traumatic brain injury, 4th ed. *Brain Trauma Foundation.* 2016; 1-9.
4. Roberts, I & Syndenham, E. Barbiturates for acute traumatic brain injury (Review). *Cochrane Database of Systematic Reviews.* 2012; 12: 1-35.
5. Marshall GT, James RF, Landman MP, et al. Pentobarbital coma for refractory intra-cranial hypertension after severe traumatic brain injury: mortality predictions and one-year outcomes in 55 patients. *J Trauma* 2010;69:275-283.
6. Bochicchio GV, Bochicchio K, Nehman S, et al. Tolerance and efficacy of enteral nutrition in traumatic brain-injured patients induced into barbiturate coma. *J Parenter Enteral Nutr* 2006;30:503-506
7. 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* 1991;29:739-741.
8. Bledsoe KA, Kramer AH. Propylene Glycol Toxicity Complicating Use of Barbituate Coma. *Neurocrit Care* 2008;9:122-124
9. Stevens AM, Then JE, Frock KM, Crookes BA, Commichau C, Marden BT, Bynnon BJ, Rebuck JA. Evaluation of feeding intolerance in patients with pentobarbital-induced coma. *Annals of Pharmacotherapy.* 2008; 42(4): 516-522.

10. Bernstein JE, Ghanchi H, Kashyap S, et al. Pentobarbital coma with therapeutic hypothermia for treatment of refractory intracranial hypertension in traumatic brain injury patients: a single institution experience. *Cureus.* 2020;12(9):e10591.
11. Stansbury BM, Kelley CJ, Rudy RF, et al. Pentobarbital coma for management of intracranial hypertension following traumatic brain injury: lack of early response to treatment portends poor outcomes. *Am J Surg*. 2023; 226(6):864-867.