Barbiturate coma as a treatment for uncontrolled diffuse cerebral edema has been explored in specific situations in the pediatric population. It is commonly used in the setting of traumatic brain injury, and other settings include Reye syndrome, near drowning, and carbon monoxide anoxia. Pentobarbital is believed to reduce ICP by reducing brain metabolism, oxygen demand, and free radial production and by altering local autoregulation. It is not believed to enhance brain oxygen tension. (Note that the neuronal effects of pentobarbital are reflected by burst suppression on EEG.)

In conjunction with other strategies to reduce high ICP, such as cooling, CSF drainage, lowering the partial pressure of carbon dioxide, and seizure prevention, barbiturate coma is a widely accepted procedure for managing diffuse cerebral edema. A critical concern with the use of pentobarbital is its adverse effects including cardiopulmonary depression, infection, liver failure, intestinal dysfunction, or immobility; therefore, pentobarbital is used selectively and with caution.

A dangerous rise in ICP can also occur in the setting of focal brain lesions of nontraumatic origin. In such a situation, pentobarbital may be a suitable agent to control an acute ICP crisis for a limited time period. We describe our experience with the use of pentobarbital as an adjunct for ICP control in 3 pediatric patients undergoing 6 operations for nontraumatic focal lesions. Special consideration was made regarding temperature control, cardiovascular stability, urine output, and infection both during and after treatment.

Methods

Three patients (Table 1) presented to our institution with large intracranial lesions: 2 choroid plexus carcinomas and 1 AVM. All were taken to the operating room for surgery.
electively for lesion resection or urgently for hematoma evacuation. Each experienced severe intraoperative brain swelling and/or postoperative elevated ICP as a result of at least one of their surgeries. In addition to undergoing standard osmotherapy, hyperventilation, and CSF drainage, patients were treated with pentobarbital to control refractory intracranial hypertension. Patients were given loading doses of 2–3 mg/kg of pentobarbital intravenously, followed by maintenance infusions of 1–3 mg/kg/hr and periodic boluses on an as-needed basis. Dose adjustments were made to keep goal ICP readings below 20 mm Hg as measured by EVD, ICP monitor (bolt), or both. Neither continuous EEG monitoring was performed nor serum pentobarbital levels were monitored in these patients. Pentobarbital therapy was maintained between 3 and 5 days postoperatively and then was discontinued. Daily CSF specimens were sent for surveillance culture in patients with external CSF drains. Urine output and cardiovascular volume status were monitored with central venous catheters, radial artery blood pressure monitors, and indwelling bladder catheters. Dopamine or nitropusside infusions were used to maintain CPPs between 60 and 80 mm Hg, and colloid boluses were used to maintain central venous pressures above 5 mm Hg. The pentobarbital therapy was discontinued after ICP stabilized below 20 mm Hg for at least 24 hours. After the discontinuation of pentobarbital therapy, ICP monitoring devices were removed, and patients were eventually transferred out of the PICU to begin rehabilitation.

In all 3 patients the measurement of serum pentobarbital levels and EEG monitoring were deferred, as the target was ICP. Use of the pentobarbital was limited by failure to control ICP or by side effects rather than by serum levels. This is the usual practice of the senior author.

Case Reports

Case 1

First Operation and Postoperative Course. A 3-year-old girl underwent a scheduled craniotomy for resection of a large choroid plexus carcinoma within the trigone of the left lateral ventricle. Because of the tumor’s size and vascularity, the surgery was marked by significant blood loss requiring transfusion of several patient blood volumes along with appropriate platelet and fresh-frozen plasma replacement. The large amount of lost blood precluded gross-total resection of the lesion, and thus we decided intraoperatively to resect the tumor in a second elective surgery in a staged fashion.

Postoperatively, the patient remained intubated and was transferred to the PICU with an EVD for CSF drainage and ICP monitoring. In the PICU the patient demonstrated intracranial hypertension of 60 mm Hg that was refractory to first-line control measures, which included hyperventilation, CSF drainage, osmotherapy with mannitol, and sedation with continuously infused fentanyl and midazolam. (Mannitol osmotherapy is the preferred choice and usual practice of the senior author.) A 2-mg/kg bolus of pentobarbital was given intravenously, and a dramatic improvement in ICP was noted. Further boluses of 1–2 mg/kg were administered intravenously for the elevated ICP on an as-needed basis (Fig. 1). As the patient’s ICP normalized, she was transitioned to a scheduled pentobarbital dose of 1 mg/kg every 4 hours until the drug was discontinued 96 hours after the initial bolus. A goal CPP between 60 and 80 mm Hg was maintained during pentobarbital therapy via dopamine infusion titrated between 2 and 10 μg/kg/min. Dopamine was required for 36 hours after discontinuation of the pentobarbital therapy and was discontinued only after sedation was stopped. However, the dopamine requirement for adequate CPP decreased from 8.0 μg/kg/min to under 6.5 μg/kg/min after the discontinuation of pentobarbital therapy.

Second Operation and Postoperative Course. The patient’s second operation was completed 2 weeks later with significantly less blood loss. Postoperatively, she was placed on an intravenous pentobarbital infusion of 1–4 mg/kg/hr (in addition to the previously mentioned osmotherapy and sedation) to maintain an ICP < 20 mm Hg. Following 72 hours of intracranial normotension, the pentobarbital infusion was discontinued. After the operation, a nicardipine infusion was required to maintain tight control of CPP in the 60- to 80-mm Hg range. Nicardipine is used per the guidelines of the local PICU. Use of this agent extended 5 days beyond the pentobarbital therapy.

An adequate urine output was maintained throughout both postoperative courses. The patient became febrile twice while on pentobarbital therapy during recovery

TABLE 1: Summary of characteristics in 3 cases of focally induced, severe cerebral edema*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>age in yrs</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>sex</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>intracranial lesion</td>
<td>choroid plexus carcinoma</td>
<td>choroid plexus carcinoma</td>
<td>ruptured AVM</td>
</tr>
<tr>
<td>no. of surgeries</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>hypotension</td>
<td>no; pressors &amp; fluids used</td>
<td>no; fluids used</td>
<td>no; pressors used</td>
</tr>
<tr>
<td>oliguria</td>
<td>no</td>
<td>no</td>
<td>mild</td>
</tr>
<tr>
<td>hypothermia</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>complications</td>
<td>urinary tract infection</td>
<td>urinary tract infection</td>
<td>no</td>
</tr>
<tr>
<td>outcome</td>
<td>good neurological recovery</td>
<td>good neurological recovery</td>
<td>good neurological recovery</td>
</tr>
</tbody>
</table>

* Control of ICP was achieved in each case, and the dose of pentobarbital in each case was below maximal.
Barbiturate coma in pediatric focally induced cerebral edema

from her first operation. All body fluid cultures remained negative at this time, and peripheral leukocytosis did not develop. Following the initial operation, a *Candida albicans* infection of the urine and the blood developed 11 and 25 days, respectively, after stopping the pentobarbital. These infections were accompanied by significant peripheral leukocytosis (peaking at 31,000 cells/μl) that resolved after treatment. Additionally, subsequent cultures became negative following 24 hours of antifungal therapy. After the second craniotomy, peripheral leukocytosis developed on the patient’s final day of pentobarbital therapy but normalized 3 days after ceasing sedation. All cultures of blood, urine, or CSF were negative following this craniotomy. Hypothermia occurred during pentobarbital use, with the lowest recorded temperature being 32.5°C. This patient made excellent neurological recoveries after both surgeries.

**Case 2**

**First Operation and Postoperative Course.** A 2-year-old boy underwent a scheduled craniotomy for resection of a large choroid plexus carcinoma of the right lateral ventricle trigone. Intraoperatively, only partial resection was achieved because of significant bleeding at the resection site and generalized brain edema as measured by postoperative EVD readings > 30 mm Hg. This high ICP was refractory to standard treatments including osmotherapy and hyperventilation. The patient was given a 2-mg/kg bolus of pentobarbital followed by a 1-mg/kg/hr infusion in the operating room. Brain swelling abated, allowing replacement of the bone flap with loose fixation over the craniotomy site.

Immediate postoperative CT scanning revealed no intraparenchymal hematoma to account for the brain swelling but did disclose significant edema and hinging of the bone flap (Fig. 2). The patient was taken to the PICU, where intravenous hypertonic saline, cisatracurium, and sufentanil infusions were used in addition to pentobarbital for ICP management. The pentobarbital infusion was adjusted between 1 and 3 mg/kg/hr to maintain an ICP < 20 mm Hg for the 72-hour duration of its use. The patient did not require pressor therapy for CPP maintenance at any point.

**Second and Third Operations and Postoperative Courses.** Second and third operations were performed to complete the tumor removal, with significantly less brain edema during these resections. A pentobarbital infusion of 1–3 mg/kg/hr was also used for ICP management for 72 hours following the second, but not the third, operation. The dose was adjusted to maintain an ICP < 20 mm Hg. The rationale for using pentobarbital after the second surgery was based on observations and experience from the first surgery: swelling was noted during the first surgery, and pentobarbital was effective in reducing ICP then and so was used after the second surgery, in which swelling was anticipated based on the first surgery. This patient did periodically require a nitroprusside infusion

![Image 1](image1.png)

**Fig. 1.** Case 1. Intracranial pressure tracings obtained after the patient’s first craniotomy. Pentobarbital boluses were initiated at postoperative Hour 2 and were continued on an as-needed basis until postoperative Hour 24, when they were transitioned to scheduled doses. h = hour.

![Image 2](image2.png)

**Fig. 2.** Case 2. Postoperative axial nonenhanced head CT depicting residual tumor and significant postoperative swelling causing midline shift and displacement of the bone flap.
following the first operation and for the majority of his recovery after the second operation. Nitroprusside was used over nicardipine in this case because of immediate availability in the intensive care unit at the time of the periodic increases in blood pressure. However, this antihypertensive was discontinued before pentobarbital therapy was completed in both instances. Periodic colloid boluses were required to augment waning central venous pressure or urine output; however, urine production never dropped below the goal level. A *Klebsiella* urinary tract infection developed (with a concomitant increase in his peripheral white blood cell count to 15,000 cells/µl) 1 day following completion of pentobarbital after the second operation. The infection was easily treated with antibiotics. Subsequent urine cultures failed to grow bacteria, and the leukocytosis normalized following treatment. Temperatures ranged from 33°C–36°C. This patient had an excellent neurological recovery following each operation.

**Case 3**

**Operation.** An 8-year-old girl underwent emergency craniotomy for evacuation of an intraparenchymal hematoma following rupture of a left frontal AVM. We performed bifrontal craniotomy and intraoperatively noted severe brain swelling that was refractory to osmotherapy and hyperventilation. A 3-mg/kg bolus of pentobarbital was administered intraoperatively, resulting in significant brain relaxation and allowing for complete hematoma evacuation. No attempt was made at AVM resection during this first operation. Due to persistent brain swelling and an intraoperative ICP > 30 mm Hg, as measured from an EVD, the craniotomy bone flap was not replaced at the end of the surgery.

**Postoperative Course.** A CT scan was obtained immediately after surgery, revealing near-complete hematoma evacuation and significant bifrontal brain edema (Fig. 3). Intravenous pentobarbital was initiated at 1 mg/kg/hr and titrated to 2 mg/kg/hr to maintain an ICP < 20 mm Hg. Treatment was continued for a total of 5 days with well-controlled ICP during that time. The patient required an intravenous dopamine infusion (dose ranging from 2–10 µg/kg/min) for the first 36 hours of her postoperative course. Thereafter, she required a nicardipine or nitroprusside infusion to maintain control of her CPP. The patient experienced mild oliguria (0.5–1.0 ml/kg/hr) for 15 nonconsecutive hours during her 120-hour pentobarbital course. Drops in urine output responded well to colloid boluses, and the patient did not experience increases in creatinine during pentobarbital therapy. There were no infectious complications during her postoperative course. She made an excellent neurological recovery.

**Discussion**

The key finding of our case series is that intraoperative and postoperative ICP elevations and brain swelling can be controlled with pentobarbital titrated to ICP. Cerebral perfusion pressure and physiological parameters were maintained in the desired range, and no direct complications from the pentobarbital therapy occurred that were unexpected in a patient in a postoperative medically induced coma. All 3 patients made satisfactory neurological recoveries. Barbiturate therapy has been explored for pediatric refractory intracranial hypertension arising from different etiologies. However, the literature yields few instances of its use for ICP control in pediatric patients with a focally induced, nontraumatic intracranial lesion (ruptured AVM or subdural empyema). Successful barbiturate therapy for massive intraoperative brain swelling related to focal lesions has been reported in the adult population. Table 2 summarizes the literature available on pentobarbital use in focal neurosurgical pathologies. These cases highlight the fact that barbiturate therapy is used as a last resort in combination with full medical and surgical management, mostly because of the adverse effects of prolonged barbiturate infusion therapy. Nonetheless, reported complications have a low rate and can be managed in the PICU setting.

Regarding the patient in Case 1, her first surgical recovery was marked by extreme intracranial hypertension (ICP = 60 mm Hg) refractory to osmotherapy, CSF drainage, and hyperventilation. Multiple pentobarbital boluses of 2 mg/kg were effective in normalizing this patient’s ICP; however, rebound ICP spikes necessitated a switch to scheduled dosing. Initial surgery for the patient in Case 2 and the only procedure for the patient in Case 3 were both marked by massive intraoperative swelling, with estimated ICPs > 30 mm Hg. Pentobarbital was effective in reducing visible intraoperative brain swelling. Intracranial pressure readings for both patients remained below 20 mm Hg, and the transition from scheduled bo-
Barbiturate coma in pediatric focally induced cerebral edema

Table 2: Reported cases of barbiturate therapy for focal intracranial lesions*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Age (yrs)</th>
<th>Pathology</th>
<th>ICP</th>
<th>Other Measure</th>
<th>Complication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kageyama et al., 2000</td>
<td>1</td>
<td>18</td>
<td>subdural empyema</td>
<td>&gt;25 mm Hg</td>
<td>surgical drainage</td>
<td>none</td>
<td>no neurological deficits</td>
</tr>
<tr>
<td>Woodcock et al., 1982</td>
<td>1</td>
<td>16</td>
<td>thalamic hemorrhage</td>
<td>20 mm Hg</td>
<td>full medical mgmt</td>
<td>none</td>
<td>pt ambulatory</td>
</tr>
<tr>
<td>Aoki &amp; Mizutani, 1985</td>
<td>1</td>
<td>38</td>
<td>MCA AVM</td>
<td>intraop massive brain swelling</td>
<td>full medical mgmt</td>
<td>none</td>
<td>good</td>
</tr>
<tr>
<td>Marshall, 1983</td>
<td>11</td>
<td>NP</td>
<td>5 AVMs; 4 hematomas; 2 penetrating injuries</td>
<td>massive intraop brain swelling</td>
<td>NP</td>
<td>2 mod disabled, 1 disabled, 2 dead</td>
<td>6 independent; 2 mod disabled; 1 disabled; 2 dead</td>
</tr>
</tbody>
</table>

* MCA = middle cerebral artery; mgmt = management; mod = moderately; NP = data not provided; pt = patient.

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Luses to continuous intravenous infusion therapy resulted in stable and more controlled ICP tracings than those in Case 1 (Fig. 4). Additionally, continuous infusion therapy allowed for more frequent and subtle adjustments in barbiturate dosing. While it can be argued that the hinging of 1 patient’s bone flap (Case 2) and the entire removal of another’s (Case 3) could have accounted for each patient’s readily controllable postoperative ICP, both experienced massive intraoperative brain swelling (and estimated ICP > 30 mm Hg, according to manual EVD measurements) despite hyperventilation, CSF drainage, mannitol boluses, and an open craniotomy defect. Of note, pentobarbital titration for each patient was based on ICP measurements and the reduction of brain swelling rather than EEG readings or serum drug concentrations. We did not find these monitoring adjuncts necessary given that our goal was ICP control, which was achieved with dosing well within acceptable guidelines.

The hemodynamic effects of pentobarbital therapy for intracranial hypertension have been studied in adults and children. Authors of both of these reports concluded that the etiology of the hypotension resulted from systemic vasodilation and low SVR rather than cardiac depression. In these studies, the hypotension experienced by children was less likely to respond to volume challenge and more likely to require infusions of pressors. Work by Kasoff et al. showed that nearly all children in that series on pentobarbital for head injury required pressors to maintain blood pressure. A systematic review of barbiturate use in head injury for adults and children demonstrated that 25% experienced significant hypotension, which lowered CPP. In our experience, only once was a dopamine infusion required for the entirety of a patient’s pentobarbital course. However, this pressor infusion was required beyond the use of barbiturate therapy and was continued (albeit at a lower dose) until the discontinuation of sedation. In another instance, a dopamine infusion (coupled with colloid boluses) was required for the first 36 hours of a patient’s 5-day pentobarbital course. Thereafter, this patient—in whom strict blood pressure parameters were desired because of her residual AVM—required nicardipine and/or nitroprusside for relative hypertension. Furthermore, antihypertensive infusions were used for blood pressure control at varying times in our other patients. This seemingly unusual finding may be related to the fact that pentobarbital dosing was titrated according to ICP rather than serum pentobarbital concentration. A relationship between increased serum pentobarbital levels and systemic hypotension has been demonstrated, and it is quite likely that the dosages used for our patients to control intracranial hypertension were less than those required to cause significantly decreased SVR. In addition, our patients responded well to pressors and volume of expanders given as required, as evidenced by our ability to maintain CPP > 60 mm Hg and our lack of serious oliguria or elevated creatinine during pentobarbital use. The effect of pentobarbital on cerebral blood flow and autoregulation has been studied in the setting of diffuse

![Fig. 4](image-url). Case 3. Graph showing the ICP tracings in a patient treated with an initial pentobarbital bolus followed by an infusion titrated for ICP control.
brain injury due to alterations in vascular tone and metabolic derangement. Work in the 1980s suggested a potential therapeutic benefit of barbiturates, although few recent data have emerged to support this effect.

Infection, although frequently described with barbiturate therapy, did not appear to be a serious complication in this small group. Of the 5 instances in which we used pentobarbital therapy, we encountered a Klebsiella urinary tract infection, which was detected 1 day after the discontinuation of barbiturates, and C. albicans infections of the urine and blood in a different patient after her first surgery at 11 and 25 days following pentobarbital therapy. Each infection was eradicated with appropriate antimicrobial therapy. While the Klebsiella infection may have been related to pentobarbital therapy, a correlation with Candida infection is seldom described in the literature. Our patients’ recoveries were not complicated by pneumonia (a common barbiturate-related infection) or leukopenia (another described complication). There is evidence of a dose-dependent correlation between barbiturate therapy and infection rates, possibly explaining our relative avoidance of this complication. Finally, each patient exhibited some degree of mild to moderate hypothermia during pentobarbital therapy. However, each responded well to warming blankets as needed, and no discernible complications were identified. Hypothermia of 32°C–33°C may be a further beneficial effect of barbiturates in this setting. In comparing ICP in normothermic and hypothermic children with traumatic brain injury, authors have found that hypothermia resulted in an almost 20% reduction in ICP, was a safe treatment, and was associated with reduced 3-month mortality. Marion et al. showed the benefits of hypothermia on ICP to be age dependent in an adult population, with younger patients showing greater reductions. Hypothermia may also have neuroprotective effects that explain the early data of barbiturate neuroprotection.

### Conclusions

We describe the use of postoperative pentobarbital for the control of refractory intracranial hypertension in children with nontraumatic focal lesions. Pentobarbital effectively lowered ICP, reduced brain swelling, and was associated with hypothermia, which may have provided added benefit in this population. Pentobarbital was successfully titrated only in response to ICP, with less than maximally tolerated doses being administered. Thus, there was no need for EEG or serum concentration data to guide therapy. We did not encounter significant cardiovascular, renal, or infectious complications associated with pentobarbital use. Since barbiturate dosing was titrated for ICP control rather than burst suppression or serum concentrations, it is possible that our dosing was high enough to reduce ICP but lower than typically required to cause significant changes in SVR or immune function. Clearly, a larger study is required to better delineate the effects of pentobarbital therapy in children with intracranial hypertension and discrete lesions. However, we believe this application of barbiturate therapy is feasible and a potential addition to other standard treatments. We suspect barbiturate coma has frequently been used to control nontraumatic cerebral edema, although the technique has seldom been reported. In highly selected situations, this therapeutic technique is probably of value.

### Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Mansour, deSouza, Kahana, Frim. Acquisition of data: Mansour, Sikorski, Kahana, Frim. Analysis and interpretation of data: all authors. Drafting the article: Mansour, deSouza, Kahana, Frim. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mansour. Statistical analysis: Mansour, deSouza, Kahana, Frim. Administrative/technical/material support: Sikorski, Kahana, Frim. Study supervision: Kahana, Frim.

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Address correspondence to: Nassir Mansour, M.D., Section of Neurosurgery, University of Chicago, MC 3026, Chicago, Illinois 60637. email: nmonim@surgery.bsd.uchicago.edu.