Pediatric cerebral resuscitation[1]

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Twenty-one pediatric patients suffered cerebral anoxic-ischemic insults and were considered candidates for cerebral resuscitation measures. Fifteen were randomly assigned to treatment protocols of either hypothermia to 30–31°C, barbiturate coma using thiopental, or a combination of hypothermia and thiopental barbiturate coma. Six patients were not assigned to treatment protocols. One patient had an isoelectric electroencephalogram and absent brainstem auditory evoked potentials and was pronounced brain dead. The other 5 patients were showing signs of rapid neurologic recovery and did not require cerebral resuscitation measures. To date there is no significant difference in outcome between the treatment categories.

Index terms: Cerebral anoxia • Cerebral resuscitation
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Cerebral resuscitation is defined as those measures used to restore central nervous system function in patients in whom these functions have been interrupted. These interruptions are usually secondary to anoxic and/or ischemic injuries to the brain (for example, cardiopulmonary arrest, shock, hypoxia), but may also include situations of increased intracranial pressure with diminished cerebral perfusion (for example, trauma or Reye's syndrome), infection (meningitis or encephalitis), or states in which demands for energy outstrip supply (for example, refractory status epilepticus or hypoglycemia).

Cerebral resuscitation is a relatively new field of medical endeavor. The initial human studies were performed in the late 1970s,[1,2] and although the results of randomized

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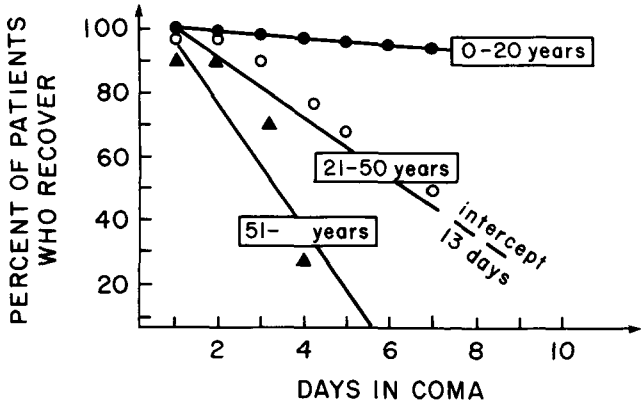
controlled studies have not yet been reported, results from the early, uncontrolled studies have generated so much excitement that some individuals have suggested that CPR (cardiopulmonary resuscitation) now be expanded to CPCR (cardiopulmonary cerebral resuscitation).

As a general rule, young brains are better able to recover from central nervous system insults than older brains (*Fig. 1*).[3] There is a limited time period within which cerebral resuscitation measures must be instituted if they are to offer any chance for success. Six hours post-insult is the generally agreed upon time period.

Methods

The initial priority in cerebral resuscitation, after the establishment of adequate oxygenation and circulation, is to differentiate patients with reversible brain injury from those with irreversible brain damage. The first step is to estimate the time of global anoxic-ischemic insult to the brain. *Table 1* delineates the method for estimating the anoxic-ischemic insult.[4]

Various clinical assessments such as the Glasgow Coma Scale (*Table 2*)[5]; neurologic examination including oculocephalic (doll's eyes), oculocaloric, and pupillary reflexes; and physiologic tests such as the electroencephalogram and brainstem evoked potentials are also useful in separating reversible from irreversible central nervous system injury. Calculation of the cerebral perfusion pressure (CPP = MABP − ICP where CPP = cerebral perfusion pressure, MABP = mean arterial blood pressure, and ICP = intracranial pressure) is also used to assess the ability of the brain to recover from the cerebral insult. It is known that a cerebral perfusion pressure of less than 20 torr or an intracranial pressure of greater than 60 torr for more than 15 minutes is incompatible with brain survival.



Percentage of patients who recovered full consciousness as a function of duration of coma and age.

Table 1. Estimation of anoxic-ischemic insult

1. Hypoxia time prior to arrest Time of severe hypotension, severe hypoxemia, or severe anemia	___ min
2. Arrest time Time without spontaneous pulse or blood pressure. Does *not* include CPR time.	___ min
3. CPR time Equals time of CPR, i.e., borderline perfusion by cardiac compressions.	___ min
4. Hypoxia time after arrest Severe hypotension, hypoxemia, or anemia following restoration of spontaneous circulation.	___ min
Total anoxic-ischemic insult time (sum of 1 + 2 + 3 + 4) =	___ min

Repeated arrest and repeated restoration of spontaneous circulation within one resuscitation effort should be stated as the sum of all times without circulation (total arrest time) and the sum of all times of hypotension, hypoxemia, and anemia (total hypoxia time), whether this occurred before or after the first or subsequent arrest.

Treatment protocol

The patient is intubated, preferably by the nasotracheal route, and paralyzed with curare or pancuronium. The initial dose of D-tubocurare is 0.5 mg/kg followed by 0.05–0.1 mg/kg/hr, and the dose of pancuronium bromide is 0.2 mg/kg as an initial intravenous dose, followed by

Table 2. Glasgow Coma Scale

	Notation
Eyes open	
Spontaneously	4
To sound	3
To pain	2
Not at all	1
Best verbal response	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Obeys commands	6
Localizes pain	5
Normal withdrawal	4
Abnormal flexion	3
Extension	2
None	1
Highest score	15
Lowest score	3

Components of the Glasgow Coma Scale for assessing impaired consciousness and coma are shown along with the notation used to derive an overall score. This ranges between 3 and 15. Adapted from Teasdale et al.[5]

0.05–0.1 mg/kg/hr. The patient is placed on controlled ventilation with a tidal volume initially of 10–12 ml/kg at a rate of 14–16 per minute, and minute ventilation is adjusted to maintain a $PaCO_2$ of 25–30 mm Hg. The PaO_2 is maintained at 100–150 mm Hg by adjusting the FIO_2, usually between 0.21 to 0.30, providing the lungs are normal. During mechanical ventilation, small intravenous dosages of morphine (0.05 mg/kg/hr) provide sedation and reduce afferent stimuli. Hemodynamic parameters are monitored by the placement of an arterial line and a Swan-Ganz catheter. Arterial cannulation of the radial or brachial artery is used for monitoring arterial blood pressure as well as for collecting blood samples for measurement of arterial blood gases and blood chemistries. A Swan-Ganz catheter is used to monitor pulmonary capillary wedge pressure and to maintain reasonable hemodynamic and renal function, at the same time maintaining the patient in a slightly dehydrated state to reduce cerebral edema. Fluid restriction is maintained at 1–1½ cc/kg/hr of D5¼ normal saline to maintain the pulmonary capillary wedge pressure at 4–6 torr. Intracranial pressure (ICP) monitoring is performed by the placement of either an intraventricular catheter, subarachnoid bolt (Richmond bolt), or fiberoptic epidural monitor (Ladd monitor). The patient is given an initial thiopental dosage of 30 mg/kg to induce barbiturate coma. Hemodynamic parameters are monitored carefully, since thiopental is a potent cardiac depressant. Continuous low dose infusion of dopamine in the range of 2–5 μg/kg/min is administered and adjusted to maintain arterial systolic blood pressure >90 mm Hg. Thiopental dosage is given as quickly as possible, preferably over a period of one hour. Once the thiopental has been administered and the hemodynamic parameters are stable, the patient is placed into moderate hypothermia by surface cooling to a temperature of 30–31°C. Core body temperature is measured on the Swan-Ganz catheter. Once the patient is in moderate hypothermia, continuous electroencephalographic (EEG) monitoring is performed, and the thiopental continuous infusion is adjusted to maintain the patient in a burst suppression to isoelectric EEG pattern.[6] The patient generally requires 10–20 mg/kg/hr of thiopental to maintain burst suppression, although larger or smaller dosages may be adequate in individual cases.[6] The thiopental dosage is adjusted to maintain the patient in burst suppression for a period of 48 to 72 hours and then is discontinued. If the EEG shows significant improvement, the patient is gradually rewarmed to normothermia at the rate of 1°C every three to four hours. If there is no improvement in the EEG, or if the EEG indicates seizures, thiopental infusion is restarted and the patient is maintained in burst suppression for an additional 48–72 hours. As the patient is rewarmed to normothermia, significant recirculation of thiopental from fatty tissues may occur, resulting in significant hemodynamic compromise. An adjustment of dopamine infusion to maintain normal hemodynamics may be needed. Once the patient has been rewarmed to normothermia, the neuromuscular paralysis is discontinued, the patient is permitted to resume spontaneous ventilation, and is then extubated. Significant increases in intracranial pressure may also be indications for reinduction of barbiturate coma for an additional 48 to 72 hours if these increases are of a significant degree and result in plateau waves greater than 30 mm Hg. A normal slight increase in intracranial pressure of 5–10 torr is to be expected with rewarming and discontinuation of neuromuscular paralysis.

The Cleveland Clinic experience over the past four years with cerebral resuscitation is shown in *Table 3*. Patients have been randomly assigned to therapies of hypothermia alone, barbiturate coma, or a combination of hypothermia and barbiturate coma. The patients have ranged in age from six weeks to 19 years of age. Two patients had refractory status epilepticus, one patient had herpes virus encephalitis, 2 patients had Reye's syndrome with intracranial hypertension, and the remaining 16 patients had cardiopulmonary arrest, with arrest plus CPR times >5 minutes and total anoxic-ischemia insult times >15 minutes. The patients in the no-therapy group were not randomly assigned to a conventional therapy

Table 3. CCF experience with cerebral resuscitation

	Therapy			
Total	Nil 6	Hypothermia 6	Barbiturate coma 3	Hypothermia + barbiturate coma 6
OUTCOME				
Died	1	3	1	1
Severe–mod. deficit				1
None–minimal deficit	5	3	2	4

group, either because initial assessment including EEG and brainstem auditory evoked potentials showed evidence of brain death (one patient), or clinical examination, EEG, and brainstem auditory evoked potentials showed that the patient was recovering rapidly and spontaneously from his cerebral insult and did not require assignment to a cerebral resuscitation protocol (5 patients). Patients in the hypothermia-alone-treatment-regimen were treated with moderate hypothermia by surface cooling to 30–31°C for 48 to 72 hours. Patients in the barbiturate-coma-alone therapy group were treated with an initial thiopental loading dose of 30 mg/kg and then placed on a continuous low dose thiopental infusion to maintain their EEG in a burst suppression to isoelectric pattern for 48 to 72 hours. Patients in the hypothermia plus barbiturate coma treatment regimen were managed as outlined in the treatment protocol.

Results

The numbers are insufficient at this stage to draw any statistical conclusions about the various therapies being tested. Because of questions about the legitimacy of historical controls, we have decided to include a control category in the study from now on consisting of patients treated according to protocol except that they will not receive barbiturates, and they will not be placed into moderate hypothermia. That is, patients will now be assigned to one of four treatment categories, either conventional therapy, hypothermia alone, barbiturate coma alone, or combined therapy with hypothermia and barbiturate coma. Although these data are preliminary and the numbers are too small to draw statistical conclusions, we believe that some patients are surviving with a better neurologic outcome than was previously experienced with conventional therapy of historical controls. This hypothesis will be formally tested.

Discussion

Cerebral resuscitation was born out of necessity. Critical care medicine and reanimatology had advanced to the stage where we could successfully resuscitate the heart and lungs of many arrest victims. However, many of these victims ultimately were in a severely compromised neurologic state or suffered brain death because the brain could not survive the same insults from which we were able to resuscitate the heart and lungs. This was especially true of the pediatric heart and lungs, which could recover from significant anoxic-ischemic injuries and arrests that left the brain dead or in a persistent vegetative state. Clearly, these could not be considered "successful resuscitations." An advance that would enable successful resuscitation of the brain after an anoxic-ischemic insult was needed. In the late 1970s significant advances in the area of cerebral resuscitation occurred, which now offer the potential for successfully resuscitating or salvaging brains that would otherwise be irreparably damaged by anoxic-ischemic insults.

Sudden complete arrest of the cerebral circulation without reperfusion results in exhaustion of oxygen stores and EEG silence within about 10 seconds and exhaustion of glucose and adenosine triphosphate (ATP) stores within about 5 minutes, at which point brain lactic acidosis has reached a maximal level.[7] Then follows homogenous dying of neurons, which, however, show clearly irreversible changes only after about 60 minutes of arrest.[8]

Total circulatory arrest of the brain for 5 minutes or longer followed by usual life support measures results in homogenous, multifocal dying of neurons and variable degrees of permanent neurologic dysfunction.[9] The outcome is the result of the initial insult plus secondary changes following reperfusion and reoxygenation. The mechanisms of brain cell damage from ischemia, hypoxemia, hypoglycemia, seizures, and trauma are believed to be similar, but therapy that is effective for one may not be effective for others. Cardiac arrest results in temporary complete global brain ischemia. "Global" refers to the entire brain in contradistinction to the focal ischemia of a stroke. The results of cerebral resuscitation are clearly dependent on a large number of factors including age, health, and nutrition before arrest; type of insult; presence of drugs or anesthetic agents before arrest, which may offer some protection; type, timing, and success of reoxygenation and reperfusion of the brain; necessity for postischemic life support; individual variations in the response to the insult and to therapy; and dosage, type, and timing of cerebral resuscitation therapy.

Both hypothermia and barbiturates are believed to work in cerebral resuscitation by reducing cerebral metabolic rate for oxygen (CMR_{O_2}) and cerebral energy consumption.[10–12] Barbiturates and hypothermia are also known to reduce

intracranial pressure.[2,13,14] It has been theorized that barbiturates may act as scavengers of membrane-damaging free radicals formed during and after anoxic-ischemic injury to the brain.[15]

It should be clear from the treatment protocol that the cerebral resuscitation measures of hypothermia and barbiturate coma are both expensive and risky. Thiopental is a potent cardiac depressant, and cardiac output and blood pressure must be monitored carefully to prevent catastrophe. Likewise, hypothermia, especially during the induction and rewarming stages, can be associated with significant cardiac arrhythmias and acidosis. The patients, therefore, must be monitored carefully in an intensive care unit whose personnel are experienced in hemodynamic monitoring, intracranial monitoring, and cerebral resuscitation measures such as induced hypothermia and barbiturate anesthesia.

Since cerebral resuscitation measures must be instituted within six hours to be effective, candidates for cerebral resuscitation should be transferred to an intensive care unit equipped and skilled in cerebral resuscitation. While one is preparing for transfer, the following measures help to protect the brain from further injury after the anoxic-ischemic insult:

> If the patient is comatose or shows signs of increased intracranial pressure, he should be intubated and hyperventilated to maintain a $PaCO_2$ of 25–30 torr and a PaO_2 of 100–150 torr; a Foley catheter should be placed; a dose of furosemide of 1–2 mg/kg should be given; an intravenous infusion of normal saline at 1–1.5 cc/kg/hr should be given; and a dose of dexamethasone at 0.5 mg/kg should be administered intravenously. If signs of intracranial hypertension occur that do not respond to manual hyperventilation, a single dose of 0.25–0.5 g/kg of mannitol over 15 to 30 minutes should be given.

Other drugs including phenytoin, benzodiazepams, narcotic antagonists, and calcium channel blockers are being researched as potential cerebral resuscitants. Recent advances in cerebral resuscitation offer the potential for significant central nervous system recovery after anoxic-ischemic or traumatic injuries to the brain. It is probably not overly optimistic to expect that a significant breakthrough in this area will be forthcoming within the next few years. Candidates for cerebral resuscitation must be stabilized and transported as quickly as possible to a center whose personnel are experienced in cerebral resuscitation.

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