What is the optimal cerebral perfusion pressure in children suffering from traumatic coma?

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Head injury is a major cause of death and disability in children. Despite advances in resuscitation, emergency care, intensive care monitoring, and clinical practices, there are few data demonstrating the predictive value of certain physiological variables regarding outcome in this patient population. Mean arterial blood pressure (MABP), intracranial pressure (ICP), and cerebral perfusion pressure (CPP = MABP – ICP) are routinely monitored in patients in many neurological intensive care units throughout the world, but there is little evidence indicating that advances in care have been matched with corresponding improvements in outcome.

Nonetheless, there is evidence that hypotension immediately following head injury is predictive of early death, and many patients with these features die with clinical signs of brain herniation caused by intracranial hypertension. Furthermore, available data indicate that a minimal and a mean CPP measured during intensive care are good predictors of outcome in survivors, but a target threshold to improve outcome has yet to be defined.

Some medical management strategies can have detrimental effects, and there is now a good case for undertaking a controlled trial of immediate or delayed craniectomy. Independent outcome in children following severe head injury is associated with higher levels of CPP. The ability to tolerate different levels of CPP may be related to age, and therefore any such surgical trial would need a carefully defined protocol so that the potential benefit of such a treatment is maximized.

KEY WORDS • cerebral perfusion pressure • intracranial pressure • head injury • coma • child

Severe head injury in children is still associated with significant mortality and morbidity rates despite advances in pediatric intensive care.^{95,105} The severity of the initial injury—usually assessed clinically based on GCS score, brainstem function, and/or systems designed to assess multiorgan failure, such as the Pediatric Risk of Mortality¹⁵—is directly associated with the incidence of death. Nonetheless, many children with such injuries do survive with a good outcome, particularly if they have not experienced shock.⁶⁸ Survival and long-term outcome may be better in children than in adults with low ICP following head injury, but patients in all age groups with ICPs higher than 20 mm Hg, whether treatable, have a worse outcome.² Intracranial hypertension is thought to cause brain damage by at least two mechanisms. First, if there are differences in pressure between the forebrain and the posterior fossa, one or both temporal lobes may herniate through the tentorium, causing direct pressure as well as reduced blood flow in the brainstem¹⁰⁴ and leading to brainstem

death, unless the pressure difference is rapidly reversed.⁶ Second, reduced CPP, the difference between MABP and mean ICP, is associated with cortical and brainstem ischemia and poor outcome in survivors, including death. Systemic hypotension is also a feature of traumatic coma in pediatric patients, and consequently CPP may be reduced for variable periods.^{58,93,96} Currently, however, there is no consensus on the level at which CPP should be maintained to optimize outcome in children with head injury.

There are specific problems in studying the pediatric population. For example, normal values of blood pressure vary with age. Nonaccidental injury is an extremely important cause of seizures, focal neuropathology, and coma in the 1st year of life¹³ and should not be forgotten as a potential origin of injury in older children. To date, most studies have been retrospective in design and have been focused on short-term outcomes, usually morbidity, because long-term follow up of survivors is difficult and expensive. In this report, we review the available data and pose strategies for future studies.

ACUTE PHASE OF INJURY

The severity of an injury has an important effect on early survival. Poor outcome, particularly death, is associ-

Abbreviations used in this paper: CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CT = computerized tomography; GCS = Glasgow Coma Scale; ICP = intracranial pressure; MABP = mean arterial blood pressure; PICU = pediatric intensive care unit.

ated with a low GCS score,^{15,63,64,129} absent brainstem function,^{78,97} and multiple trauma.^{63,64,75} A CT scan can also be an important predictor of patient outcome in its ability to demonstrate mass lesions or diffuse swelling.^{42,73,101} After severe head injury, ICP is often raised due to either mass lesions such as extradural, subdural, or intracerebral hemorrhage, which are present in approximately one quarter of severely head injured children,² or diffuse swelling.^{3,61} Patients with rapidly treated extradural or subdural hemorrhage may fare as well as those with nondiagnostic CT scans,⁴² although not in all cases.⁶³ Those with intraparenchymal or intraventricular hemorrhage or diffuse swelling have an increased chance of disability as well as death.^{33,34,42,66} Evidence-based guidelines for the evacuation of intraparenchymal hematomas have not yet been established for children.⁷¹ Cerebral blood flow may be significantly reduced as ICP rises, and cerebral metabolic rate and cerebral oxygen extraction are maximal shortly after injury in children.¹¹⁵ This means that the brain is very vulnerable to ischemic injury at this stage. Severe early intracranial hypertension may be associated with brain death within a few hours,⁹² although a good outcome is possible in such cases.⁹⁹ Many children also experience hypotension immediately following an injury, either as a direct effect of head injury or due to hemorrhage.⁹³ Hypotension is an important predictor of outcome,^{19,66,69,96} although improvements in emergency management procedures have enabled some patients who have experienced shock to survive.⁶³ The average initial blood pressure in head-injured children is higher than normal levels in age-matched children.²⁸ Although there is an absolute requirement to raise blood pressure in children whose level falls below the 5th percentile for their age and there is a good case for volume expansion and/or vasopressors in those with normal blood pressure for their age,¹³⁵ these principles are not advocated by all.^{12,50} Many patients suffer other secondary brain insults²⁰ (for example, coagulopathy¹³² and hyperglycemia²¹) before they receive intensive care, and these insults may influence outcome. Hypoxia may be more highly associated with poor outcome in survivors⁷⁸ than death,⁹⁶ although this assertion is controversial.⁹¹ In addition, anemia may play a role in patient outcome.⁷² The effect of early posttraumatic seizures on morbidity and death is uncertain: they were associated with survival in one series¹³⁵ and poor outcome in another.²¹ Prophylactic therapy may be associated with reduced mortality rates.¹³⁰ Emergency care should be organized to optimize CPP during the golden hour immediately following head injury given that there is some evidence that this is beneficial. For example, the length of time between injury and admission to the PICU appeared to influence outcome in survivors in one series.²¹

PROLONGED INTENSIVE CARE

Most patients with who survive the first few hours after severe head injury require several days of intensive care, and ICP is usually measured during this time.^{74,113} The clinical and physiological variables on admission are less predictive of the level of disability in survivors. Instead, the GCS score 24 to 72 hours after injury is a better predictor of good outcome.^{18,78} Although children develop

multiorgan failure less often than adults,¹⁴ those with multiple injuries, particularly if the chest is involved, are vulnerable to secondary insults such as hypotension and hypoxia.⁷⁸ In one series delayed injury was documented on a CT scan in 41% of patients¹²² and was associated with multiple injuries and clotting disorders. Other possible mechanisms of secondary or progressive injury which may be associated with intracranial hypertension include arterial stroke (caused by carotid artery or vertebral artery dissection),^{10,32,110} venous sinus thrombosis,^{123,126} vasospasm,⁷ and seizures.⁸¹

PATHOPHYSIOLOGICAL FEATURES

Both ICP and CPP may remain stable for long periods of time in unconscious patients, but may then fluctuate unexpectedly. There are several mechanisms that maintain CBF in the face of changing blood pressure and increased oxygen extraction when CPP is low. Autoregulation is the most crucial of these mechanisms important in compensating for temporary derangement in normal brain tissue and is apparently preserved in the majority of head-injured children.^{85,114} Note, however, that failure of autoregulation has been associated with poor outcome.¹¹⁴ Any attempt to define an optimal level of CPP for an individual patient of any age must therefore take this pathophysiology into account, even if it cannot be measured in a particular patient.

Sustained plateau or A waves were first described by Lundberg, et al.,⁷⁰ but not until much later was the vasodilatory cascade hypothesis put forward by Rosner and Becker¹⁰⁷ to explain their occurrence. These latter investigators asserted that CPP may be unstable at values between approximately 50 and 90 mm Hg. When MABP (or CPP) is high, most of the resistance occurring in response to a change in pressure takes place in the larger (> 200 μ m) pial and intracerebral vessels; however, at values lower than 90 mm Hg, the smaller (< 100 μ m) cerebral vessels also dilate. Although autoregulation may be preserved, slight decreases in blood pressure are associated with rapid vasodilation causing marked increases in cerebral blood volume and therefore in ICP.¹⁰⁷ In adults, ICP plateau waves did not occur at CPP values higher than 90 mm Hg. The plateau waves are usually self-limiting because the vessels reach maximal dilation and a compensatory Cushing response increases CBF and ICP initially. The increase in MABP causes vasoconstriction and then a decrease in ICP. The Cushing response is variable and may fail after a series of pressure waves⁶² or, if the systemic circulation is compromised, because of poor cardiac function or fluid restriction.¹⁰⁸

As CPP decreases below the lower limit of autoregulation, that is, between 40 and 60 mm Hg,^{79,134} oxygen extraction increases.⁴⁹ Eventually, if CPP declines further, the vessels become maximally dilated (vasoparalysis) and they cannot respond to any increase in metabolic demand by increasing CBF. As a result, ischemia will occur if the capacity to increase oxygen extraction has been exceeded. The precise values for CPP at which these changes occur are uncertain and may vary in different circumstances, depending, for example, on whether there has been a recent previous plateau wave or seizure. At values of CPP less than 30 mm Hg, the vessels collapse and there is severe and irreversible ischemia.

MONITORING ICP AND CPP IN CHILDREN

In pediatric head trauma, although it is clear that potentially avoidable secondary insults are common,^{16,47} as they are in adults,⁴⁸ defining an optimal CPP to avoid them remains an area in which there is no absolute consensus. Children's blood pressure levels are normally lower, but there are very few data on normal levels of ICP in children; thus a normal level of CPP must be derived.⁴⁷ There are very few studies in which investigators have looked at using ICP or CPP for the prediction of survival or outcome in pediatric patients with coma (traumatic or non-traumatic). Those that are available are relatively small and include patients with different mechanisms of injury (focal or diffuse) and treatment strategies for sustained intracranial hypertension; thus, determining a level of ICP or CPP at which corrective action should be taken is very difficult.

Intracranial Pressure, CPP, and the Prediction of Death

Although defining a safe threshold has proved elusive, several authors have shown that ICP and CPP measurements from long-term monitoring are good predictors of death in pediatric patients with traumatic coma.^{17,31,40,47,56,99,125} In one series, a sustained ICP greater than 60 mm Hg was associated with death in all patients; there was only one survivor among those with a prolonged ICP higher than 50 mm Hg and that patient was disabled.⁹⁹ In another study, a lower mean ICP was associated with survival.¹³⁵ Data from this study also indicated that survival was more likely in those with a maximal systolic blood pressure greater than 135 mm Hg, although previous studies have demonstrated that hypertension may be associated with poor outcome in survivors.^{12,50} In a very large series focused on adults and children, Luerssen, et al.,⁶⁹ found hypotension to be a good predictor of death; children with hypertension had the best outcome compared with adults, who fared best with normal blood pressure.

A mean CPP less than 40 mm Hg predicted death in all children in one study.³¹ These results agree with Changaris and colleagues¹⁸ data, which demonstrated that a mean CPP less than 40 mm Hg on Day 1 in adults and in children as young as 3 years of age, predicted death. These authors also found that patients with a mean CPP of less than 60 mm Hg for longer than 8 hours on Day 2 postinjury had a higher mortality rate. There is considerable discrepancy in the threshold reported in different series. For example, Hackbarth, et al.,⁴⁰ found that the inability to maintain a CPP greater than 50 mm Hg on the 1st day in the PICU appeared to predict death, whereas in the series of Jones and colleagues,⁴⁷ death was associated with a wider mean range of CPP, that is, 2 to 65 mm Hg.

Cerebral Perfusion Pressure and the Prediction of Morbidity in Survivors

There are few data on the prediction of outcome in survivors. A minimal CPP of less than 30 mm Hg sustained for more than a few minutes is rarely compatible with intact survival, whatever the origin of injury.³⁶ Nonetheless, in the absence of published data, it would be unwise

to use any specific cutoff in terms of the minimal CPP or duration of low CPP to make decisions about the withdrawal of treatment in an individual patient, especially given that good outcome has been documented in patients with a minimal CPP of less than 30 mm Hg for a short time period (unpublished data).^{30,37} Additional information about a likely prognosis may be obtained at the patient's bedside by using neurophysiological or CBF techniques.^{53,54}

In a combined series of head-injured adults and children, Changaris, et al.,¹⁸ found that a mean CPP higher than 90 mm Hg on Day 2 postinjury was associated with a good outcome, but they also acknowledged that children might be able to tolerate a lower mean CPP, although a threshold was not defined. A better outcome in survivors has been associated with a higher mean and minimal CPP in most^{16,47,56} but not all¹²⁵ series involving pediatric patients. Regardless, the recommended safe level has varied, perhaps because of differences in the patient populations or the methods of analysis.

In one of the few studies with a long-term follow up of the survival of children following head injury (50 patients), Kieslich and colleagues⁵² found that of 17 children with a minimal CPP less than 50 mm Hg, two thirds had moderate or severe disability. Jones, et al.,⁴⁷ noted that the duration of age-specific disruption in CPP was the best predictor of outcome and that a reduction in CPP was commonly caused by a decrease in MABP as well as an increase in ICP. These authors asserted that attempting to maintain CPP within the physiological range for age might improve outcome. Chambers, et al.,¹⁷ who used receiver-operator curves, examined the sensitivity and specificity of ICP and CPP in relation to independent outcome in 84 children with head injury. These investigators proposed that, although it was necessary to allow for unexpected fluctuations and measurement errors, the minimal acceptable CPP might be lower in children (60 mm Hg rather than the 70 mm Hg recommended for adults).¹⁰⁹ In fact, there are data from adults with traumatic coma indicating that a CPP of greater than 60 mm Hg has little influence on outcome.⁴⁸ Chambers and coworkers¹⁶ and Jones and colleagues⁴⁷ asserted that in children with diffuse head injury and in whom sudden increases in ICP were relatively rare, it might be more important to measure blood pressure than ICP. This may also be the case in infants who have been nonaccidentally injured, especially given that in this group, minimal CPP and MABP were related to outcome, but maximal ICP was not.⁹

There are also pertinent data from patients with non-traumatic coma. Tasker, et al.,¹²⁷ found in a group of children unconscious for a variety of reasons that those with a minimal CPP of less than 38 mm Hg all fared very poorly, but that there were some patients with a poor outcome in whom a CPP below this value was not noted. There is evidence that a high ICP and a low CPP are also associated with a poor prognosis in Reye syndrome,⁴⁶ hepatic failure,⁵ central nervous system infections,^{36,53,82,87,88,103} and focal⁸¹ and global ischemia (including that from near drowning).^{11,53,65,90,111} In a series including children with traumatic and nontraumatic coma, the mean CPP during the entire monitoring period was the only variable that predicted survival and good outcome.⁵⁶ A mean CPP less

than 65 and 50 mm Hg during the first 6 hours predicted poor outcome and death, respectively.⁵⁶

MANAGEMENT OF CPP

Medical Therapy

It has proved more difficult to show that improving CPP advances outcome with currently available medical management. It is generally agreed that a child should be nursed flat, with his or her head in the midline (so that venous drainage from the head is not obstructed) and his or her head positioned either flat or tilted up to 30°. The patient should be handled as little as possible, and nursing procedures such as suction should be performed with caution.

Unfortunately, many of the techniques for reducing ICP rapidly in an emergency have detrimental effects when used over a longer time period, and there are very few data from randomized controlled trials in children with outcome in survivors as the end point. Controlled trials of medical treatment for intracranial hypertension have been conducted mainly in adults with head injuries, but these have demonstrated no overall benefit of treatment with steroid or barbiturate agents, hyperventilation, or hypothermia. There is no evidence that prophylactic hyperventilation prevents intracranial hypertension,⁸⁴ but there is evidence that CBF may be reduced below the ischemic threshold with the aid of hypocapnia in unconscious children.¹¹⁹ Fluid restriction has been shown to be potentially harmful in children with meningitis.¹⁰⁰ Mannitol may reduce spikes of ICP very rapidly and acts either as an osmotic diuretic or by reducing cerebral blood volume. As with hyperventilation therapy, there is no evidence that the regular prophylactic use of mannitol is beneficial, and results from one study showed an increase in the length of the PICU stay in patients who had received mannitol, with no evidence of improved outcome.¹³⁵ Hypertonic saline may have advantages⁹⁴ and has been associated with a decreased duration in the PICU stay in a randomized trial in children,¹¹⁷ but there are concerns that there is a risk of central pontine myelinolysis and long-term follow-up data are awaited.

For barbiturate coma, the risk of hypotension probably outweighs any useful effect in reducing ICP. Drug levels may remain high for several days after administration of the drug has been discontinued, making the clinical diagnosis of brain death impossible. Reducing body temperature, even by a small amount, reduces cerebral metabolic rate considerably, and there is evidence for an additional beneficial effect on ischemic brain tissue. One major advantage is that hypothermia is easily reversible. There is a risk of neutropenia and infection,^{11,45} but benefit has been indicated in head-injured patients, perhaps in reducing ICP rather than as a neuroprotective agent.⁴⁴ Data from one controlled trial in adults revealed no benefit,²⁴ possibly because of unexpected age and center differences and because patients in the hypothermia arm required increased fluids. The ongoing Hypothermia in Pediatric Head Injury Trial⁴³ (a randomized controlled trial in children, which is also exploring the use of a wide range of outcome measures) will provide useful information.

In adults, two alternative strategies are currently proposed for the management of intractable intracranial hy-

pertension.^{89,108,109,121} Rosner and colleagues^{108,109} suggested that medical strategies to reduce ICP and maintain CPP higher than 70 mm Hg may improve outcome. There is evidence from nonrandomized studies in adults that patients with a CPP greater than 70 mm Hg have a better outcome, but standardized protocols have been designed to maintain CPP above this level. The problem is that the evidence to support such a strategy is inconclusive. Robertson, et al.,¹⁰⁷ found that although cerebral ischemia was reduced using a similar protocol that included the maintenance of normocapnia, survival was not improved and adult respiratory distress syndrome was more common in the treatment arm. If autoregulation is preserved, increasing blood pressure does reduce ICP in children with head injury.⁸⁵ Because children are relatively protected from multiorgan failure, maintenance of a relatively high CPP might improve neurological outcome without any increase in other complications; demonstrating this, however, requires definition of a target CPP in different age groups^{16,17,47} and a randomized trial. An alternative volume-targeted strategy has been proposed by Nordström and coworkers^{89,121} and involves the maintenance of a normal colloid osmotic pressure (with blood or albumin transfusion) in combination with a reduction in intracapillary hydrostatic pressure to encourage increased resorption of intracerebral water and therefore a reduction in cerebral edema. Note that there are few data on the efficacy of this management strategy in children.

Surgical Management

Mass lesions may require surgical treatment, and drainage of cerebrospinal fluid via the ventricular or lumbar route is probably beneficial,⁶⁷ although there are few data proving this. Early clinical experience with radical craniectomy in the management of severe head injury was mixed,^{26,51,57,102,116,133,137} and enthusiasm was particularly dampened by the demonstration of increased cerebral edema experimentally²⁵ and upward herniation of the human brain postmortem after circumferential craniectomy.²³ Part of the discrepancy among study data may reflect the age of the patients, the timing of surgical decompression, the presence of a mass lesion such as a subdural hematoma, and the severity of brainstem compression as indicated by papillary responses or respiration. The original data were collected before advances in anesthetic agents, operative techniques, and intensive treatment of such patients.

Subtemporal decompression has also been advocated in patients who fail to respond to medical management. Alexander, et al.,⁴ pointed out that one could expect an increase in intracranial volume of up to 33 cm³ from a subtemporal decompression. Gower, et al.,³⁸ looked at a retrospective series of patients with severe head injuries who would not have been expected to survive because of a failure to respond to intensive treatment including chemoparalysis, hyperventilation, mannitol, or pentobarbital therapy. Ten patients who had undergone subtemporal decompression suffered substantially lower morbidity and mortality rates (40%) compared with a group treated only with medical therapy (82%).

Surgical decompression has continued to be performed by personnel in several centers by using a variety of techniques with variable results. This procedure was usually

undertaken for signs of incipient transtentorial herniation within the first few hours postinjury or for intractable hypertension despite maximal medical therapy during intensive care.^{29,35,39,59,60,77,86,98,112} Social rehabilitation is certainly possible in these cases,¹ and there has been a recent resurgence of interest in the use of decompressive craniectomy as part of a protocol for the early management of raised ICP in head injury.¹³⁶ Given that signs such as pupillary dilation occur late in brainstem compromise,⁶ it would be more helpful to use early physiological measurements (CPP and ICP) rather than clinical signs or imaging studies, whose direct relationship to ICP is problematic. In one series, craniectomy reduced intraventricular pressure by mean of 50%, and opening the dura mater further reduced intraventricular pressure by 35%.¹³⁸ Monitoring of ICP and tissue oxygenation may give sufficient warning of impending deterioration to allow for a later craniectomy.¹²⁴

For a number of reasons, including the ethical dilemma of obtaining consent in the acute phase following head injury and a lack of consensus on the criteria for the most appropriate procedure, randomized controlled trials have proved very difficult to organize. Although young age is one of the best predictors of good outcome, children may be excluded from future studies, in part because there are few data on the relationship among ICP, CPP, and outcome in this group. Results of several case series have demonstrated a benefit from unilateral and bilateral edema for traumatic^{27,41,83,117,118,120} and nontraumatic^{8,53–56,76,80} coma in the pediatric population, including those with an ICP greater than 30 mm Hg in the context of a subdural hematoma after a shaking injury.²² A recent randomized controlled trial of early craniectomy after head trauma in a pediatric population¹²⁸ appeared to show a clear benefit, with seven of 13 patients remaining independent after craniectomy compared with two of 14 patients randomized to conventional treatment. Nonetheless, questions remain about the interpretation and extrapolation of data from this small pilot study, including the precise indications for craniectomy, inclusion and exclusion criteria, the best operation to perform, and whether the dura should be opened. To plan a trial that would include a pediatric population (Randomised Evaluation of Surgery with Craniectomy),¹³¹ perhaps in which were compared surgical decompression with a protocol to maximize blood pressure, the ICP and CPP thresholds that could distinguish good from poor outcome in children of different ages must be determined.

CONCLUSIONS

In conclusion, independent outcome in children following severe head injury is associated with higher levels of CPP. Note, however, that the sensitivity of both CPP and ICP may vary with age and that younger children may be able to tolerate lower levels of CPP and/or higher levels of ICP while still achieving independent outcomes. Further research in this important area is urgently needed to increase the evidence base for clinical practice.

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Manuscript received October 31, 2003.

Accepted in final form November 12, 2003.

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