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Raised intracranial pressure during central nervous system infection: what should we do about it?

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Normal cerebrospinal fluid (CSF) pressure in children at the time of lumbar puncture is positive in relation to atmospheric pressure, with 10th to 90th percentile of 11.5 to 28 cm water, or 8.7 to 21.2 mm Hg, respectively (1). Intracranial pressure (ICP) is the pressure of CSF inside the cerebral ventricles, which is determined by cerebral blood flow (CBF) and CSF circulation. The Davson equation describes this relationship and states that ICP is the sum of sagittal sinus pressure and the product of CSF formation rate and resistance to CSF outflow (2). Normal values for sagittal sinus pressure, CSF formation rate, and resistance to CSF outflow are 5 to 8 mm Hg, 0.3 to 0.4 mL/min, and 6 to 10 mm Hg/mL/min, respectively. Measured ICP is often greater than the calculated value because of a vascular component, which is probably a result of pulsation in the arterial bed and the interaction between pulsatile arterial inflow and venous outflow curves, cardiac function, and cerebral vasomotor tone (3). All of these interrelationships may be altered in critically ill comatose patients with central nervous system (CNS) infection. These abnormalities may also be compounded by: brain swelling, edema and increased cerebral blood volume (CBV); focal cerebral perfusion deficits and variable levels of CBF and cerebrovascular carbon dioxide (CO₂) reactivity; and, cerebral vasculitis (4–7). The net result is raised ICP along with significant risk of brain tissue herniation and ischemic syndromes, and death (8–10).

In this issue of the *Journal*, Kumar et al. (11) report a study from Chahdigarh, India, in comatose children (aged 1 to 12 years) with acute CNS infection undergoing invasive ICP monitoring. The authors addressed the pragmatic question of whether to target level of ICP (<20 mm Hg) or whether to target level of cerebral perfusion pressure (CPP >60 mm Hg, the difference between mean arterial blood pressure (BP) and mean ICP) with intensive care unit therapies. The authors' conclusion from this randomized controlled trial (RCT) is that the CPP goal, rather than ICP goal, is superior and results in better rates of morbidity and mortality. This study has significant bearing on both adult and pediatric critical care practice. However, there are important considerations that warrant further discussion.

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First, there were major therapeutic consequences of the different strategies used in this RCT. The primary aim of targeting level of CPP meant that systolic BP was targeted to the 95th percentile for age and hence there was more frequent use of inotropes. The primary aim of targeting level of ICP meant that any systolic BP >5th percentile was considered acceptable and as a consequence these patients had lower BP. In addition, the ICP group was exposed to hyperventilation and osmotherapy more frequently than the CPP group. At the start experimental interventions both groups had similar level of mean BP, around the 90th percentile for age. Yet, over subsequent hours the ICP group had mean BP that decreased to the 50th percentile, whereas the CPP group had mean BP that increased to the 95th percentile. Over this same period, the mean ICP in all patients fell to a level within the normal range (1), albeit lower in the ICP group. We need to learn more from these observations by Kumar et al. (11) and what they tell us about life-threatening CNS infection. For example, in relation to the age- and sex-specific standards in BP in healthy children, these patients were nearly 'hypertensive' at presentation. Better outcomes were observed in those where this 'near-hypertensive' level was maintained. Perhaps, then, higher targets for mean BP and systolic BP should be used in these critically ill children (12). Perhaps, too, this 'near-hypertensive' BP at presentation is a response to lower than normal cerebral oxygen delivery and perfusion deficits (5, 6), and we would do well not to ignore the apparent target that homeostasis is setting.

Second, we need to reconsider whether the ICP-directed therapies – mannitol and hyperventilation – lack benefit or are potentially detrimental. In regard to osmotic therapy for meningitis, to date, there have been four RCTs (comprising 1091 adult and pediatric participants) comparing glycerol with a control. Collective data from the trials do not demonstrate any benefit on death, or on death and neurologic disability combined; the Cochrane review in 2013 concluded that osmotic diuretics should not be given to adult and pediatric patients with bacterial meningitis (13). In the report by Kumar et al. (11), a greater proportion of the ICP group received mannitol, which may also have resulted in BP lowering and potential detrimental effects (see above). Whether the more frequent and greater duration of hyperventilation in the ICP group was also potentially detrimental is unknown. For example, at presentation, most patients with acute bacterial meningitis hyperventilate spontaneously (14), and we do not know what level in arterial CO₂ partial pressure should be targeted during mechanical ventilation in those with baseline hypocapnia (15). Normally, acute hyperventilation reduces CBF and CBV. In life-threatening CNS infection this response is used to reduce ICP, but the associated fall in CBF and CBV will only render the brain at risk of focal or global ischemia if cerebrovascular CO₂-reactivity is intact. Two studies in adults with acute bacterial meningitis have demonstrated that short-term hyperventilation does not enhance regional abnormalities in CBF, nor does it alter cerebral metabolic rate for oxygen (5, 6). Taking all this evidence together, there is little to support the routine use of mannitol and hyperventilation in neurocritical care for life-threatening CNS infection.

Last, it might appear from the current report (11) that all unconscious pediatric patients with CNS infection should now undergo ICP monitoring so that we can target CPP with our therapies. In 2006, a large secondary analysis of administrative data for hospitalized children with meningitis in the United States (US) revealed no association between patient survival

and the use of ICP monitors (16). In March 2009, US adult and pediatric neurosurgeons appeared skeptical of the evidence to use ICP monitors in children with meningitis; out of 420 respondents to a survey sent to 728 neurosurgeons, only one-third felt there was sufficient evidence to monitor ICP (17). Will the current report by Kumar et al. (11) add weight to the clinical decision to place an ICP monitor in a comatose child with acute CNS infection? The reason now for requesting such monitoring is in order to target CPP >60 mm Hg with the use of inotropes. However, one could equally argue that what is actually needed is BP monitoring and targeting systolic BP at the 95th percentile for age and sex. Such an approach is more likely to be achieved worldwide and implemented in settings with limited resources (18). The quandary that we are left with is reminiscent of the resource-issues (19) surrounding a recent RCT of ICP monitoring in traumatic brain injury (20). In that study from South America intensive care focused on maintaining monitored ICP at 20 mm Hg was not shown to be superior to intensive care based on serial cranial computed tomography (CT) scans and clinical examination. Do we really need an ICP monitor in comatose patients with acute CNS infection or would an arterial line alone be as effective, since that is what is actually determining changes in treatment?

In conclusion, Kumar et al. (11) are to be commended on conducting an informative and instructive study that will reinvigorate this field of neurocritical care. The implications of other important observations will need further study: the range of CT findings in those with raised ICP; over the first 24 hours, the similarity in pattern in mean CPP and mean ICP in both the ICP-group-survivors and the CPP-group-non-survivors, yet profound difference in outcome; and, the time course of lack of responsiveness to therapies in the CPP-group-non-survivors in the period 24 to 48 hours.

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