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Analgesia, Sedation and Intracranial Pressure: questioning our approach in pediatric traumatic brain injury

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In this issue of the *Journal*, Welch et al. (1) present a work that comes in the tradition started by Nils Lundberg in 1960 (2) and latterly exemplified by so-called “multimodality monitoring in neurocritical care” (3). Lundberg's thesis demonstrated that continuous monitoring of cerebral ventricular fluid pressure and inspection of graphic recordings of pressure variations over time “give information of practical diagnostic significance” (2). We now rely on complex algorithms and summary mathematical functions and indices to evaluate changes in intracranial hydrodynamic and hemodynamic function (4), but the idea is the same – graphic continuous recording with description of intracranial pressure (ICP) variations.

Welch et al. (1) describe time-series analyses and findings from a retrospective study into the effect of doses of sedatives and analgesics on ICP and cerebral perfusion pressure (CPP, the difference between mean blood pressure and mean ICP) in pediatric patients after severe TBI. The authors found that bolus dosing of midazolam and fentanyl were ineffective at treating episodic intracranial hypertension. This finding will come as no surprise to practitioners who care for adult patients after severe TBI, since lack of effect is well described in that population (5-10). One key issue, however, that makes this new report (1) noteworthy is that in contrast to adult practice – in which standard sedation is a combination of propofol and midazolam, with morphine, fentanyl and alfentanil/sufentanil as the main analgesics (11) – propofol is not available for continuous infusion in the pediatric intensive care unit (12). Readers may wonder whether, given these data, our sedation and analgesia strategy should now change. We should therefore focus on the why, what and when of bolus dosing of sedatives and analgesics in pediatric patients after severe TBI and explore in more detail the clinical context of the cases studied by Welch et al. (1).

In the mechanically ventilated pediatric patient we use sedatives and analgesics because of the potential complications of routine intensive care management when awake (e.g., ventilator-patient-dyssynchrony, agitation, anxiety, and pain). These complications may result in worsening intracranial hypertension through a remote mechanism such as impairment of cerebral venous return because of a Valsalva maneuver or rise in intrathoracic pressure, or through a direct mechanism such as change in cerebral blood flow, CPP, and

cerebral metabolic rate for oxygen. Infusion of short-acting sedative and analgesic medications should both avoid the complications described above, as well as allow for periods when clinical neurological assessments can be carried out during interruptions in drug delivery. Additional bolus doses may be given in anticipation of a procedure, or in response to an obvious change in state with agitation, anxiety or pain. In the series reported by Welch et al. (1) there were 31 patients with 413 episodes of ICP >20 mm Hg lasting at least 5 minutes and, of these, 211 episodes were treated with a bolus dose of midazolam and/or fentanyl. The authors do not know why ICP was raised during these episodes, but simply that bedside attendants chose to administer either midazolam (high-dose >0.1 mg/kg or low-dose 0.1 mg/kg) and/or fentanyl (high-dose >1 µg/kg or low-dose 1 µg/kg) as immediate treatment. Given that there are six possible therapeutic combinations here, there must be qualitative differences in the individual clinical scenarios that made bedside attendants grade the indication for treatment, and select one or two drugs, at high- or low-dose. The authors are unable to provide this information, or even whether all endpoints of interest (e.g., pain and agitation) as well changes in ICP and CPP summary indices may have responded to the administration of sedative and/or analgesic medication.

Two aspects of the “when” of treatment with sedatives and analgesics are also highlighted by the report from Welch et al. (1), but before discussing these we should briefly review the management of intracranial hypertension in patients after severe TBI. Generally, we adopt a “3-tiered” or “3-staged” approach to management that utilizes various treatments to target different mechanisms (13, 14). *Tier 1* therapies in the mechanically ventilated patient undergoing ICP monitoring includes: elevating the head-of-the-bed to 30° in order to improve cerebral venous outflow; intermittent ventricular cerebrospinal fluid drainage; and, administration of short-acting sedatives and analgesics so as to allow the patient to tolerate bedside intensive care procedures and nursing treatments. *Tier 2* is marked by an escalation to *pro re nata* dosing of hyperosmolar therapies and neuromuscular blockade. *Tier 3* is the stage when anesthetic dosing of barbiturates, or propofol, along with continuous infusion of neuromuscular blocking agent are used. Salvage or “rescue” treatments for diffuse cerebral edema such as decompressive craniectomy or induced hypothermia, are considered after standard treatments used in *tier 3* have failed to control ICP. Escalation in treatment from *tier 1* to *tier 2*, or from *tier 2* to *tier 3*, is recommended when there is failure to control ICP or CPP within target ranges.

In the context of such a “tiered” approach to treatment we should first note that no treatment was given in 202 of the 413 episodes of ICP above 20 mm Hg lasting at least 5 minutes. Why not? To calibrate the reader to potential severity-of-illness here, consider the entry criteria to the Eurotherm3235 trial of hypothermia for intracranial hypertension after TBI in adults: an ICP >20 mm Hg for at least 5 minutes after *tier 1* treatments (14). We do not have any answers from the authors, but again there must be qualitative differences in the individual clinical scenarios that made bedside attendants decide not to intervene. The quandary that we are left with is reminiscent of the situation that the South American treatment of ICP trials (15) left us with, and the new concerns surrounding use of ICP monitoring after severe TBI (16). In the South American studies, maintaining monitored ICP at 20 mm Hg was not superior to intensive care based on serial cranial computed

tomography scans and clinical examination. Taken together, there is clearly something else important about the “vital sign” of ICP >20 mm Hg for at least 5 minutes that we are not able to characterize with a number, i.e., when not treating the physiological parameter doesn't matter.

Second, close inspection of the data in the report by Welch et al. (1) also tells us the circumstances of administration of sedatives and analgesics in relation to *tiers* of therapy. The majority of the patients were undergoing *tier 2* or *tier 3* therapies at the time of receiving bolus doses of sedative and analgesic medications. That is, the report is really about the use of these agents during *tiers 2 and 3* practices rather than during *tier 1* management. Again, to provide a severity-of-illness context here, in the Eurotherm3235 trial (14) approximately 1-in-3 patients screened were not eligible for recruitment because they were responding to *tier 1* therapies and did not exhibit episodes of ICP >20 mm Hg for at least 5 minutes – presumably because of response to sedatives and analgesics (likely, propofol and an opiate) and the other measures (see above). Welch et al. (1) found in their model of change in ICP cumulative pressure-time product >20 mm Hg, comparing epochs 15 minutes before with 15 minutes after administration of fentanyl and/or midazolam, that these agents resulted in a net increase in “intracranial hypertension burden”.

In conclusion, the novel report by Welch et al. (1) gives us much to think about in regard to the management of intracranial hypertension in pediatric patients after severe TBI. It does not tell us to give up using fentanyl and midazolam during *tier 1* therapies. Rather, it may be telling us that these agents are ineffective at reducing ICP during *tier 2 and 3* therapies – if that is the reason behind individual bolus dosing. We clearly need more data of the type reported here, but we also need contemporaneous clinical annotation in future studies. We the future we should be investigating the reasons why these agents are used, and whether there are alternative strategies beyond using our currently available benzodiazepine and opiate combination. Welch et al. (1) should be commended on the breakthrough that they now present in the *Journal*. It will lead to more debate and discussion, and hopefully more pediatric studies in the tradition of Lundberg and others (2, 3).

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