Fever Control in the NICU: Is There Still a Simpler and Cheaper Solution?

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Published online: 26 October 2011
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Evidence from experimental studies and clinical observations has clearly demonstrated the negative impact of fever after brain injury [1]. Until the recent arrival of temperature modulating devices, previous attempts to aggressively treat fever with pharmacological agents such as acetaminophen or ibuprofen had often failed [2]. As with any therapy, however, the promise of improving outcomes by maintaining normothermia is weighed down by some of the complications associated with aggressive fever control itself [3]. Given that therapeutic normothermia is not a benign intervention, it is important to continue to refine the methods by which to reduce temperature burden. In this issue of *Neurocritical Care*, Mullins et al. remind us to not to disregard the importance of pharmacological approaches to aggressive fever control.

Endogenous pyrogens released by leukocytes in response to infection, drugs, blood products, or other stimuli cause fever by stimulating cerebral prostaglandin-E synthesis and as a result raise the hypothalamic temperature set point. Antipyretic agents, including acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAID), are believed to block this process by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain, resulting in a lowering of the hypothalamic set point [4]. Traditionally, the effectiveness of antipyretic agents was believed to be tightly linked to conditions where thermoregulation is intact; therefore, more likely to be ineffective in

brain-injured patients with impaired thermoregulatory mechanisms. In fact, trials of utilizing either acetaminophen or ibuprofen failed to demonstrate a reliable reduction in the burden of fever [5, 6].

However, none of these previous trials had utilized a combination of acetaminophen and ibuprofen. In their study, Mullins et al. compared monotherapy with high doses of ibuprofen or acetaminophen against a combination of the two agents. The primary endpoint was a reduction in temperature burden at 6 h, and they found a modest incremental reduction with the combination of acetaminophen and ibuprofen, without an increase in adverse effects related to bleeding or renal insufficiency.

These findings are limited by the small sample size of the study, and their use of hourly oral temperature measurements (rather than continuous core temperature measures). The reduction in burden was seen without the addition of temperature modulating devices, though 13 patients were excluded due to the concomitant use of surface or intravascular cooling devices. It is not clear whether the lack of temperature reduction led to the early use of a device. Their study design was to measure temperature burden for only 6 h, and as a result precluded the ability to ascertain the full duration of temperature reduction with combination therapy. It would have also been interesting to see the differential effect of ibuprofen on markers of inflammation as has been shown in a recent normothermia trial utilizing an intravascular cooling device [7].

Nonetheless, this study demonstrates that even in the era of advanced temperature modulating devices, there is still a place for traditional pharmacological approaches in aggressive fever control. There are inherent advantages to continuing to try new pharmacological approaches, namely, ease of use and reduced cost. Antipyretics are cheap and do not require additional pharmacological

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interventions for shiver control and sedation. It is unlikely that a combination of drugs will eliminate our reliance on devices. Temperature modulating devices are here to stay. However, an aggressive fever control protocol utilizing high dose antipyretics may partially lower the fever burden, resulting in less work of a device and ultimately reduce the incidence of moderate to severe shivering. In addition, this approach could increase our ability to aggressively treat fever in those we are reluctant to place on devices out of concern for over sedation (e.g., nonmechanically ventilated subarachnoid hemorrhage patient).

However, more evidence is required before we can make informed decisions about the best management strategy for aggressive fever control. Determining the appropriate combination of these drugs require further investigations into the optimal timing, dose, and duration. With the recent addition of intravenous forms of both of these drugs, the use of parenteral boluses or infusions should also be tested. Finally, all of these approaches with temperature devices and/or advanced pharmacological dosages still require a randomized controlled trial to prove their ability to improve outcome in febrile brain-injured patients.

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