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EDITORIAL

Continuous intravenous NSAID administration for fever control

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Brain-injured patients commonly experience fever, and hyperthermia may lead to poor outcome in these patients, although a direct causative link has yet to be established. The impact of fever on patients in a neurocritical care unit has been evaluated, and after controlling for severity of illness, diagnosis, age, and complications, fever was found to strongly associate with an increased length of ICU and overall hospital stay, as well as higher mortality and worse overall outcome [1]. Patients with neurological injuries may experience fever from a variety of causes, most commonly including pneumonia, urinary tract infection, medications, and deep venous thrombosis, and these entities may contribute to worse outcomes for non-neurologic reasons.

Excellent biological evidence exists for a direct impact of fever specifically on neurological outcome. On a local level, fever produces increased levels of excitatory amino acids (e.g. glutamate and dopamine), free radicals, lactic acid, and pyruvate [2]. There is an increase in ischemic depolarizations as well as blood–brain barrier breakdown. Enzymatic function is impaired and cytoskeletal stability is reduced. These events lead to increased cerebral edema, with possible reductions in cerebral perfusion pressures, as well as larger volumes of ischemic injury [3, 4]. A variety of brain injuries may be impacted by fever, including ischemic stroke [5], subarachnoid hemorrhage (SAH) [6], intracerebral hemorrhage [7], traumatic brain injury (TBI) [8], and global ischemic injury from cardiac arrest [9].

Much of the recent neurocritical care literature has focused on induced hypothermia for treating brain-injured patients. The neuroprotective effects of induced hypothermia have been demonstrated for cardiac arrest patients [10], and show promise in ischemic stroke patients as well [11]. However, induced hypothermia was not found to be definitively effective in treating TBI patients [12], and has only been studied in a limited fashion in SAH patients. Thus, the goal of therapy for these patient for the time being remains fever control, hopefully preventing the harmful sequelae of fever on the neurological injuries in these patients without causing significant adverse effects.

In this issue of *Neurocritical Care*, Drs. Cormio and Citerio report the results of their study of the use of a continuous infusion of diclofenac sodium to control fever in 22 comatose patients with either TBI or SAH (12 and 10 patients, respectively). The goal of this study was to compare the efficacy of the continuous infusion of diclofenac (12 patients) with extemporaneous boluses of NSAIDs (10 patients) for overall fever control. The primary outcome was the length of time with a temperature >38°C, and secondary outcome measures included the effect of each therapy on intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), and heart rate, and to monitor the adverse effects of each strategy.

The patients treated with the continuous diclofenac infusion had a significantly decreased burden of time with fever, and although the area under the curve was not described, this group also had lower mean and maximum temperatures. In the secondary outcome measures, they separated the groups into patients with elevated ICP (≥25 mmHg) before randomization, and those without ICP elevations. Only in patients *without* pre-randomization ICP elevation was there a significant effect on the secondary variables: the group randomized to the continuous diclofenac infusion showed improvements in ICP, CPP, and MAP. Finally, the authors report no increase in adverse

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events, including gastrointestinal or intracranial bleeding. They conclude that the continuous infusion of diclofenac is more effective than intermittent NSAID administration for controlling fever, and leads to improvements in select populations for cardiovascular and cerebrodynamic parameters.

The authors are to be applauded for this contribution to our understanding of effective and safe means of controlling fever in brain-injured patients. However, there are several limitations to this study that must be taken into consideration. First, the sample size was small, limited to only comatose patients (GCS≤8), and was further broken down to patients with TBI or SAH; all of these factors limit the generalizability of the results. It remains to be seen if this is an effective therapy in patients with less severe clinical states, or with other disease etiologies, such as ischemic stroke or primary intracerebral hemorrhage. TBI patients represent a very heterogeneous group, and with only 12 patients in this group one must consider the potential influence of comorbid illnesses and concomitant injuries to other parts of the body. Similarly, SAH patients may have significantly different coexisting variables, including comorbid illnesses and varying degrees of myocardial suppression, which certainly may have influenced the hemodynamic variables measured in this trial.

Furthermore, there was no placebo group, and the type of NSAID used in the control group (diclofenac, ketoprofene, or proparacetamol) was at the discretion of the attending physician, lending the control group to significant heterogeneity of treatment. This certainly should be taken into account in such a small trail, in which variability of therapy may have had significant effects on the outcomes. This again becomes poignant when one takes into consideration that this trial included such therapies as extreme hyperventilation (to a pCO_2 of <25 mm Hg) to treat ICP elevations, a therapy which is not commonly practiced. The authors contend that the use of a placebo arm in this trial would have been unethical, as it has become routine practice to aggressively treat fever in brain-injured patients. However, this is not a subtle point, as an effect on outcome with fever control in this population has not been definitively proven, and the therapies used to treat fever are not entirely benign.

Why was the ICP positively influenced only in those patients with pre-randomization *non*-elevated ICP? The question is difficult to answer, but the authors propose that the patients who already had ICP elevations were less susceptible to the effects of fever, or that the effects of fever would be ''masked'' by the already pathologically affected brain. One could argue that the patients who already had an elevated ICP would benefit the most from fever control to preserve neurological outcome. Unfortunately, the study was not powered to discern a difference in outcomes, as measured by the Glasgow Outcome Scale. It would likely take a significantly larger trial to see an effect on overall neurological outcome.

However, multiple important points can be gleaned from this study. There appears to be a clear and consistent effect of controlling fever by the continuous diclofenac infusion, and the effect (or rather, lack of a negative effect) on the hemodynamic parameters (MAP, CPP, ICP) in comparison to the control group is a highly attractive secondary outcome finding. Comatose TBI and SAH patients are highly susceptible to the negative effects of impaired hemodynamics, and this therapy argues for significant stability of these parameters when the continuous diclofenac infusion is used. The control group did not fare as well, with significant reductions in MAP and CPP. It remains to be seen whether this is a cost-effective means of treating fever, and whether the results can be applied to other patient populations.

Multiple methods of fever control are currently available. (Table 1) Traditional pharmacological methods, including the intermittent administration of NSAIDs, are

Table 1 Methods of controlling fever

Method	Advantages	Disadvantages
NSAIDS	Inexpensive, widely available	Poor efficacy, bleeding, hepatotoxicity, nephrotoxicity
Cooling blankets, ice packs	Inexpensive, widely available	Uncomfortable, difficult to regulate
Cold solution infusions	Inexpensive, widely available	Requires large fluid boluses, electrolyte disturbances
Peritoneal cooling	Inexpensive, widely available	Invasive, not commonly practiced, carries increased risk of infection, peritonitis
Cooling helmet	Provides local cooling effect, limits systemic effects	Expensive, not widely available, effective only for reducing brain temperatures minimal degrees
Intravascular catheters	Rapid temperature control, effective regulation	Invasive, expensive, carries increased risk of infection, DVT
Cooling vests	Rapid temperature control, effective regulation	Expensive, risk of skin breakdown with prolonged use

often only minimally effective, and may have significant side effects, including hypotension and bleeding [13]. Surface cooling with ice packs and cooling blankets can induce shivering, and may impair patient comfort. Other effective therapies include peritoneal cooling or infusions of ice-cold solutions, which are quite effective in reducing temperature quickly. Finally, more advanced techniques include the use of selective head cooling via a helmet device, intravascular cooling via a catheter approach, and surface cooling with an adhesive vest device. These devices carry the added benefit of continuous temperature control, but are more expensive.

Temperature control in the neurocritical care population is an area of active investigation, and neurointensivists continue to explore the appropriate patient populations to study, the proper cooling techniques to employ, and the relevant outcomes to assess. Many questions remain: What is the optimal temperature to attempt to achieve? For how long should aggressive fever control be undertaken? What is the proper population in which to apply induced hypothermia, and for what duration? What are the most effective, safest, and most cost-effective techniques to employ in temperature modulation? Surely, temperature regulation will remain a ''hot'' topic in the neurocritical care community for years to come!

References

1. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 2004;32:1489–95.
2. Stocchetti N, Protti A, Lattuada M, et al. Impact of pyrexia on neurochemistry and cerebral oxygenation after acute brain injury. J Neurol Neurosurg Psych 2005;76:1135–9.
3. Morimoto T, Ginsberg MD, Deitrich WD Zhao W. Hyperthermia enhances spectrin breakdown in transient focal cerebral ischemia. Brain Res 1997;746:43–51.
4. Baena RC, Busto R, Dietrich WD, et al. Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. Neurology 1997;48:768–73.
5. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. Stroke 2000;31:410–4.
6. Oliveira-Filho J, Ezzedine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology 2001;56:1299–1304.
7. Schwartz S, Häfner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. Neurology 2000;54:350–4.
8. Stocchetti N, Rossi S, Zanier ER, et al. Pyrexia in head-injured patients admitted to intensive care. Int Care Med 2002;28:1555–62.
9. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007–12.
10. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
11. De Georgia MA, Krieger DW, Abou-Chebi A, et al. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. Neurology. 2004;63:312–7.
12. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med. 2001;244:556–63.
13. Dippel DW, van Breda EJ, van der Worp HB, et al. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial. BMC Cardiovasc Disord 2003;3:1–8.