Intensive Care Med (2015) 41:1126–1128
DOI 10.1007/s00134-015-3798-x

EDITORIAL

Kees H. Polderman

An injured brain needs cooling down: yes

Received: 8 March 2015
Accepted: 2 April 2015
Published online: 14 May 2015

For a contrasting viewpoint, please go to
doi:10.1007/s00134-015-3844-8.

K. H. Polderman (✉)
Department of Critical Care Medicine, University of Pittsburgh Medical Center, 3550 Terrace Street, Scaife Hall/6th floor, Pittsburgh, PA 15261, USA
e-mail: k.polderman@tip.nl; PoldermanKH@upmc.edu

A large proportion of patients with any type of acute brain injury will develop fever within the first few days of their ICU or hospital stay [1]. The causes are variable. Often, the patient gets so-called central (non-infectious) fever, as a direct consequence of the brain injury itself. In addition, brain-injured patients are at exceptionally high risk of infections; apart from the risk of complications such as aspiration pneumonia (due to decreased consciousness and diminished protective reflexes), brain injury can directly induce immune dysfunction (mediated through the vagal nerve, with efferent signals inhibiting pro-inflammatory cytokine production), leading to an immunocompromised state with increased susceptibility to infections [2, 3].

When fever occurs, temperature in the brain itself rises even more than systemic temperature. This is due to excess heat generated by ongoing destructive processes in the brain. These include neuroinflammation, influx of excess calcium into injured brain cells leading to hypermetabolism, free radical production, and trapping of the heat in injured areas due to local oedema formation and vascular blockage ("cerebral thermopooling") [2]. These processes lead to a general "overheating" of the brain, with additional temperature elevations in injured areas [2]. Numerous clinical studies have demonstrated that brain temperature exceeds core temperature by 1–2 °C in patients with severe brain injury, with temperatures in injured areas exceeding core temperatures by up to 4 °C [1, 2].

The higher brain temperature (especially in injured areas) can cause additional neurological damage [2]. This has been conclusively demonstrated in numerous animal experiments, where experimentally induced brain injury increases significantly when animals are externally warmed; this phenomenon is independent of the initial severity of injury, and is especially pronounced if hyperthermia coincides with a period of ischemia [2, 4]. Conversely, fever control mitigates brain injury in animal models [2].

As would be expected when studying these pathophysiological processes, hyperthermia (regardless of its cause) is independently associated with increased risk of adverse outcome in all types of acute neurologic injury. Clinical studies in ischemic stroke (AIS), subarachnoid haemorrhage, intracranial haemorrhage (ICH), traumatic brain injury (TBI), and cardiac arrest have demonstrated independent correlations between fever and worse neurological outcome, higher mortality, and increased length of stay [1]. This has been documented in dozens of observational studies [1]. To cite just a few: patients with AIS who develop fever have larger infarct volumes (OR 3.23) and greater neurological deficits (OR 3.06) [5]; increased risk of haemorrhagic transformation (OR 7.3) [6]; and a 3.4- to 6-fold increase in risk of adverse outcome [7, 8]. Fever in cardiac arrest patients increases the risk of unfavourable outcome by a factor of 2.3 per °C temperature increase above 37 °C [9]. In patients with ICH the proportion of time spent at temperatures greater than 37.5 °C within the first 72 h is independently associated with poor outcome [10]. One study even reported that peak body temperature predicts mortality in patients without cerebral damage [11].

This huge detrimental impact is partly explained by the pathophysiology outlined above, with brain temperature far exceeding core temperature and heat trapping in injured areas [2]. In addition, fever causes a generalized increase in metabolic rate (7–10 % per °C increase in core temperature), with corresponding increases in minute ventilation and oxygen consumption [1, 2]; this can be detrimental depending on the patient's condition.

Clearly, under certain conditions (particularly if acute brain injury is present), fever can be highly destructive. So, is fever a purely harmful phenomenon that should be suppressed in all critically ill patients?

The answer is an emphatic no. Fever is one of the protective responses of the body, associated with a pro-inflammatory state that can help the body fight infections. Fever can inhibit the growth of certain species of bacteria, while simultaneously stimulating immune cell function and enhancing antibody and cytokine synthesis [12]. Several studies suggest that suppression of fever with antipyretics in patients with influenza can adversely affect outcome [13].

Clearly, fever should not always be suppressed. In some clinical situations it can be protective and helpful, while in other conditions it is destructive and harmful. This balance may shift even within the same patient, with protective effects of a febrile response outweighing harm in some phases of a disease, while harm outweighs benefits in other phases. As so often in critical care medicine, there are no absolutes.

Likely, the overwhelming majority of patients with acute brain injury are at risk if fever develops, and will benefit from strict fever control (or, in some cases, therapeutic hypothermia). In contrast, patients with severe infections who need an inflammatory response might not benefit from fever control, and could even suffer adverse consequences.

What if both conditions are present simultaneously? This, potentially, is the case in patients with intracranial infections such as meningitis and encephalitis. Here the febrile response could have clear benefits (enhanced inflammatory response), but also cause harm (temperature-induced increase in brain injury). At this time, it is unclear whether and when some or all of such patients would benefit from fever control.

A study by Saxena and co-workers published recently in this journal [14] partially addresses this question. The authors performed a retrospective analysis of two large intensive care databases in Australia, New Zealand and Great Britain, to assess correlations between the highest recorded temperature in the first 24 h of ICU admission and outcome. They found that for patients with CNS infections elevated peak temperature in the first 24 h is not associated with increased risk of death compared to normothermia (37–37.4 °C). In fact, in the UK registry moderate temperature elevations were associated with lower risk of death, suggesting that a moderate febrile response could be protective at this stage. In contrast, and in keeping with previous observations, fever was linked to adverse outcome in TBI and in all types of stroke, although significant increases in mortality were seen only when peak temperature exceeded 39 °C [14].

The study is limited by its retrospective nature, and especially because overall temperature burden could not be determined (only peak temperature was assessed). In addition, only the first 24 h were considered; while beneficial effects of fever might outweigh harm in the acute stages of CNS infection, this might change in later phases of the disease as antibiotic effects kick in (so that the patient's fever response becomes less important), especially if brain oedema develops which can be worsened by hyperthermia [1, 2]. Nevertheless, these data strongly suggest that patients with intracranial infections suffer no adverse consequences of, and might benefit from, a moderate febrile response, and that temperature control in early stages of CNS infections should only be considered at extreme temperature elevations (greater than 39.5 °C), or perhaps in patients with brain oedema.

Should this lead us to view fever in brain injured patients in a different light, and to reconsider our overall strategies of fever control at least in patients with infectious causes for fever? In my view the answer is a resounding no. In the vast majority of patients with acute brain injury, the harmful effects of fever clearly outweigh any potential benefits. Fever is a two-edged sword: the immune-enhancing effect helps in combatting infections, but stimulates neuroinflammation and other destructive processes that can add to brain damage. Most infections can likely be controlled through other means in most patients, but fever-induced additional brain damage could be permanent.

The decision on which effect is more important for the patient should be individualized.

Central fever should always be treated. If the cause is infectious but the source lies outside the CNS and can be treated without too much difficulty, fever should still be suppressed, as the destructive effects on the brain will likely outweigh any potential gains in infection control in the vast majority of patients.

There is some clinical evidence that the patient's febrile response is not needed in the context of proper supportive care and appropriate antibiotic therapy, even in patients with severe infections. A multicentre trial randomized 200 patients with septic shock to fever suppression or no temperature control, and found more rapid shock reversal and a 16 % absolute reduction in 14-day mortality in patients subjected to fever control [15]. Thus, fever control seems to be at least safe (and perhaps beneficial) even in septic shock patients; presence of infections should not deter us from controlling fever in brain-injured patients. CNS infections may be the exception to this general rule, especially in the early stages. Further (prospective) studies will be needed to clarify the

role of temperature in evolving CNS infection, and to assess the possible role of fever control in later stages, particularly in patients who develop brain oedema.

Temperature is a key physiological parameter in critically ill patients. It should be regarded in the same way (and controlling it granted the same importance) as blood pressure, heart rate, and ventilation parameters. As with these other parameters, usually normal values are good; in some situations, below-normal levels (hypothermia) may be beneficial; and sometimes, when patients need a boost of their immune response, fever could be advantageous.

But in most situations, an injured brain is an overheated brain, and absolutely needs cooling down.

Conflicts of interest None applicable.

References

1. Polderman KH (2008) Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 371:1955–1969
2. Polderman KH (2009) Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 37:S186–S202
3. Tracey KJ (2007) Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007(117):289–296
4. Wang CX, Stroink A, Casto JM, Kattner K (2009) Hyperthermia exacerbates ischaemic brain injury. Int J Stroke 4:274–284
5. Castillo J, Davalos A, Marrugat J, Noya M (1998) Timing for fever-related brain damage in acute ischemic stroke. Stroke 29:2455–2460
6. Leira R, Sobrino T, Blanco M et al (2012) A higher body temperature is associated with haemorrhagic transformation in patients with acute stroke untreated with recombinant tissue-type plasminogen activator (rtPA). Clin Sci (Lond) 122:113–119
7. Azzimondi G, Bassein L, Nonino F et al (1995) Fever in acute stroke worsens prognosis: a prospective study. Stroke 26:2040–2043
8. Phipps MS, Desai RA, Wira C, Bravata DM (2011) Epidemiology and outcomes of fever burden among patients with acute ischemic stroke. Stroke 42:3357–3362
9. Zeiner A, Holzer M, Sterz F et al (2001) Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 161:2007–2012
10. Schwarz S, Hafner K, Aschoff A, Schwab S (2000) Incidence and prognostic significance of fever following intracerebral hemorrhage. Neurology 54:354–361
11. Kiekkas P, Kiekkas P, Velissaris D et al (2010) Peak body temperature predicts mortality in critically ill patients without cerebral damage. Heart Lung 39:208–216
12. Mackowiak PA (1994) Fever: blessing or curse? A unifying hypothesis. Ann Intern Med 120:1037–1040
13. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R (2010) The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis. J R Soc Med 103:403–411
14. Saxena M, Young P, Pilcher D et al (2015) Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med. doi:10.1007/s00134-015-3676-6
15. Schortgen F, Clabault K, Katsahian S et al (2012) Fever control using external cooling in septic shock—a randomized controlled trial. Am J Respir Crit Care Med 185:1088–1095