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Treatment of Fever After Stroke: Conflicting Evidence

Sylwia E. Wrotek, PhD, **Wieslaw E. Kozak, PhD**, **David C. Hess, MD**, and **Susan C. Fagan, PharmD.**
Program in Clinical and Experimental Therapeutics (S.E.W., D.C.H., S.C.F.), University of Georgia College of Pharmacy, Charlie Norwood Veterans Administration Medical Center (S.E.W., S.C.F.) and Department of Neurology, Medical College of Georgia, (D.C.H., S.C.F.) Augusta, GA; and the Departments of Immunology (S.E.W., W.E.K.), Institute of General and Molecular Biology, Nicolaus Copernicus University, Torun, Poland

Abstract

Approximately 50% of patients hospitalized for stroke develop fever. In fact, experimental evidence suggests that high body temperature is significantly correlated to initial stroke severity, lesion size, mortality, and neurologic outcome. Fever occurring after stroke is associated with poor outcomes. We investigated the etiology of fever after stroke and present evidence evaluating the efficacy and safety of interventions used to treat stroke-associated fever. Oral antipyretics are only marginally effective in lowering elevated body temperature in this population and may have unintended adverse consequences. Nonpharmacologic approaches to cooling have been more effective in achieving normothermia, but whether stroke outcomes can be improved remains unclear. We recommend using body temperature as a biomarker and a catalyst for aggressive investigation for an infectious etiology. Care must be taken not to exceed the new standard of a maximum acetaminophen does of 3 g/day to avoid patient harm.

Keywords

stroke; fever; hyperthermia; inflammation

Introduction

In a healthy human, the normal core body temperature is 37°C and is tightly controlled by the thermoregulatory center in the hypothalamus. Effective thermoregulatory defenses, which can be grouped into autonomic and behavioral responses, make body temperature difficult to disrupt. For a thorough review of this topic, the reader is referred to a previously published article.[1] Sometimes, however, thermoregulatory control is impaired by serious illness. Between 40% and 61% of patients who experience stroke develop fever, and those patients with fever are far more likely to die within the first 10 days after a stroke than those with lower temperatures.[2, 3] Clinical data support that body temperature higher than 37.5°C significantly correlates with poor outcomes.[2, 4–7] This was confirmed in two separate meta-analyses that showed that high body temperature after stroke is associated with significantly higher morbidity and mortality rates compared with normothermic patients, independent of the origin of the temperature elevation.[8, 9]

There are two distinct causes of high body temperature: fever and hyperthermia. Very often, authors use the terms fever and hyperthermia interchangeably. However, it is important to

Correspondence to Dr Susan C. Fagan, UGA Clinical Pharmacy, CJ-1020 Medical College of Georgia, 1120 15th St, Augusta, GA 30912-2450. sfagan@mail.mcg.edu.

make the distinction between them, because the origin and influence of these syndromes are different.[10] Hyperthermia represents a failure in thermoregulation in which there is uncontrolled heat production (e.g., during exercise), poor heat dissipation (e.g., wearing protective clothing in a hot and humid environment), or an external heat load (e.g., sunbathing or sauna) that does not involve a thermoregulatory set point.[11] Hyperthermia represents an unregulated rise in body temperature in which microbial products and pyrogenic cytokines are not directly involved and against which standard antipyretics are ineffective. Fever, however, is a complex reaction to pyrogens that not only causes the body's thermoregulatory set point to rise, but also simultaneously stimulates an acute-phase reaction and activates numerous metabolic, endocrinologic, and immunologic systems and behaviors.[12, 13] It is likely that most cases of elevated body temperature after stroke are due to fever, not hyperthermia.

Rationale for Treating Stroke-Associated Fever

Animal studies show that a rise in body temperature after experimentally induced cerebral ischemia produces more extensive brain damage[14, 15] and that hyperthermic ischemic rats tend to remain unresponsive and die soon after ischemia.[16] When brain temperature was elevated to 40°C for 3 hours within 24 hours after middle cerebral artery occlusion, the resulting cortical infarct volume enlarged dramatically (~6.4-fold), as did the total infarct volume (3-fold). In addition, neurobehavioral recovery in animals with fever was worse compared with animals with normal body temperatures.[14]

The relationship between the intensity of fever and stroke outcome or infarct volume is strongest within the first 24 hours; the earlier that fever develops, the worse the cerebral damage is expected to be.[3] Furthermore, high body temperature causes the transformation of ischemic penumbra into infarction, increases blood-brain barrier breakdown,[17] and increases apoptosis and the inflammatory response.[18, 19] One group of authors supported the notion that fever control may be neuroprotective in patients with subarachnoid hemorrhage.[20] They showed that induced normothermia was associated with a significant reduction of cerebral metabolic distress. The authors concluded that active fever control is a reasonable therapeutic strategy after subarachnoid hemorrhage.

Etiology of Fever After Stroke

Elevation of inflammatory markers in the acute phase of ischemic stroke is a well-known phenomenon and may result from infection with exogenous microorganisms or from the endogenous inflammatory response of brain repair. Invading inflammatory microorganisms such as bacteria release pyrogens including lipopolisaccharide, peptidoglycans and muramyl peptides that activate leukocytes to release endogenous pyrogens, including the interleukins 1 and 6, tumor necrosis factor-α and interferon-γ. These cytokines trigger liberation of arachidonic acid from membrane phospholipids, activation of cyclooxygenase, and subsequent production of prostaglandins such as prostaglandin E_2 (PGE_2). Prostaglandin E_2 alters the thermoregulatory set point in the anterior hypothalamus, and the sympathetic response that ensues raises the core temperature to the febrile set point.[21, 22]

Infectious Fever

In most cases, infection is the cause of fever after stroke. One group of authors examined 119 patients hospitalized after ischemic stroke; 25% of these patients had fever (temperature > 38°C) within 24 hours of experiencing stroke symptoms, and 32% had a body temperature higher than 37.5°C within 48 hours after ischemic stroke.[23] Authors suggested that the probable causes of fever within 48 hours after ischemic stroke included pneumococci, streptococci, *Escherichia coli*, enterococci or parainfluenza virus and influenza virus type A.

They concluded that most fever (83%) can be explained by infectious or chemical aspiration pneumonia.[23] Pneumonitis after aspiration is frequently followed by early bacterial infection even within the first 48 hours.[24, 25]

Noninfectious Fever

In severe stroke, massive tissue necrosis can elevate body temperature.[7] Another cause of noninfectious fever can be the presence of blood in the brain. Within hours after hemorrhage, lysis of blood cells leads to accumulation of free blood constituents like hemoglobin and hemoglobin degradation products such as heme.[26, 27] Basic science studies have demonstrated that heme infused into the rat brain provokes fever.[28] In previous work, we demonstrated that intracerebroventricular injection of heme-L-lysinate causes a dose-dependent elevation of temperature in rats.[29] This was accompanied by elevation of the PGE_2 level in cerebrospinal fluid, which was prevented by an infusion of antibody against PGE_2; however, administration of indomethacin did not prevent the heme-induced fever-like response. These data indicate that heme-induced fever is a PGE_2-dependent response.

Distinguishing Between Infectious and Noninfectious Fever

Fever occurs most often within the first two days after a stroke.[2] However, its cause is not always easy to identify. Some authors emphasize that timing of fever can indicate origin.[3, 30] Although fever resulting from stroke-related pathologic processes starts within 24 hours of stroke symptoms, fever due to infection emerges at later time points. This suggests that if preexisting infection is excluded, early fever in stroke patients can indicates a neurological origin.

One study reported that serum C-reactive protein levels may prove useful in determining the etiology of fever, at least in patients with neutropenia.[31] However, in another study, patients who had evidence of infection had the highest plasma C-reactive protein concentrations of the cohort on admission, and the concentrations either decreased or did not increase markedly during the first week.[32] The changes in cytokines after stroke are very similar to those changes after acute bacterial or viral infection or surgical intervention.[33, 34] Because of this, cytokines cannot be used as factors to distinguish noninfectious fever from infectious fever. In patients with small stroke infarct volumes, it has been suggested that a marked increase in body temperature, C-reactive protein level, or white blood cell count should be taken as an indicator of infection.[35] Patients with large infarcts often exhibit a moderate increase in inflammatory parameters without evidence of infection.[35] Moreover, patients with larger lesions may show a slower decrease of inflammatory markers because of the higher level of cerebral necrosis present in a larger injury.[35]

After quantifying inflammatory markers such as C-reactive protein, fibrinogen and leukocyte count, it appears that ischemic stroke does not evoke a typical acute-phase response in most patients.[36]

Treatment of Fever After Stroke

Standards and Guidelines

European stroke specialists view the monitoring of body temperature as an essential component of care in stroke units.[37] The European Stroke Initiative's recommendations for stroke management include treating body temperature higher than 37.5°C, searching for a possible infection (site and etiology), and starting tailored antibiotic treatment. Similarly, the recommendations of the European Stroke Organization are to monitor body temperature and begin a search for concurrent infection when temperature is above 37°C.[38] Both groups recommend acetaminophen to treat fever, without specific doses mentioned.

The American Stroke Association guidelines for patients with ischemic stroke recommend antipyretic agents if the body temperature is high, both in ischemic[39] and hemorrhagic[40] stroke but no temperature threshold or treatment strategy is recommended. This uncertainty is reflected in the variability of standing orders for body temperature elevation in "Get with the Guidelines" hospitals (http://www.amhrt.org/HEARTORG/HealthcareResearch/GetWithThe GuidelinesHFStroke/GetWithTheGuidelinesStrokeHomePage/Stroke-Clinical-Tools-Library_UCM_303743_Article.jsp). In five separate examples of acute ischemic stroke standing orders, there were five different order sets dealing with elevated temperature that ranged from no order to acetaminophen 1000 mg every 4–6 hours for temperature greater than 38.6°C. In hospitals where acetaminophen is recommended for fever, doses from 325–1000 mg up to 6 times/day were recommended (not to exceed 4 g/day).

Experimental and Clinical Trials

Multimodal Cooling—In a prospective randomized study of the effectiveness of an air-circulating cooling blanket for fever control in patients who had a stroke, the patients were treated with either acetaminophen and air blanket every 4 hours or acetaminophen and air blanket therapy.[41] Treatment with an air-circulating cooling blanket after 24 hours did not effectively reduce body temperature in febrile patients in the neurologic intensive care unit compared with treatment with acetaminophen alone (44% vs 36% effectively cooled, respectively). Moreover, 12% of patients did not tolerate the air blanket. This demonstrated that therapy with acetaminophen alone or with the air blanket was effective in controlling fever in less than half of febrile patients.

In a large observational study of a hypothermia blanket used in patients with body temperatures of 102.5°F (39.17°C) in the intensive care unit, the authors concluded that this method was not more effective than other cooling methods.[42] For blanket-treated and control patients, the mean cooling rate was the same (0.028°F/hr). However, use of these blankets was associated with greater temperature fluctuations and more rebound hypothermia than in other methods.

Another alternative is endovascular cooling, which leads to rapid induction, stable maintenance and controlled rewarming. Cooled saline that circulates around an intravascular catheter may be used to prevent fever or to induce hypothermia. In a prospective randomized trial, conventional treatment of fever (acetaminophen and cooling blankets) was compared with conventional treatment plus an intravascular catheter-based heat exchange system (Alsius, Irvine, CA).[43] The authors found that a catheter-based cooling system significantly improved fever reduction in patients in the neurologic intensive care unit and was more effective in controlling fever than conventional means. Another group of investigators evaluated the feasibility of inducing and maintaining moderate hypothermia with the use of an intravenous cooling device.[44] The pace of cooling was a mean ± SD of 1.40 ± 0.6°C/hour, and the target temperature was reached after 3 ± 1 hours. During hypothermia, the maximum temperature observed was 33.4°C, and the minimum temperature was 32.2°C.

In a prospective study that evaluated a surface cooling method (blanket with a flow of cool air) to induce hypothermia, patients' body temperatures were decreased from a mean of 36.8°C (normothermia) to 35.5°C, and hypothermia was maintained until 4 hours after therapy (36.8°C vs 35.5°C).[45] Mortality at 6 months after stroke was 11% lower for patients treated with surface cooling than for control patients (temperature on admission 36.9°C). Most published studies focus on hypothermia (32–35°C) as a target temperature. Depending on the method used, hypothermia can be achieved after 4–11 hours.[44–47] However, achievement of normothermia could also be sufficient to decrease stroke complications.[46] One group of authors found that in patients with large supratentorial hemorrhage, coexistent pyrexia significantly increased mortality compared to normothermic patients.[5] This study

suggests that achieving normothermia might be sufficient to improve the outcomes of stroke and fever.

Pharmacologic Treatment

Antibiotics: Antibiotics should be administered early if an infectious origin is suspected, but prophylactic use of antibiotics is not currently recommended. It is important to note that frequent use or inappropriate use of antibiotics to prevent infections can result in an increase in antibiotic-resistant bacteria. Research performed on mice and showed that preventive antibacterial treatment completely averted the development of fever, significantly reduced mortality, and improved neurologic outcome after experimental stroke.[48] Similarly, a study performed in patients with stroke demonstrated that prophylactic antibiotic therapy with mezlocillin plus sulbactam over 4 days after acute severe ischemic stroke was well tolerated, and decreased the occurrence, magnitude, and duration of fever.[49] In addition, the therapy lowered the rate of infection and may even have be associated with an improved clinical outcome.

However, the Early Systemic Prophylaxis of Infection After Stroke (EPIAS) study was prematurely stopped because levofloxacin neither prevented poststroke infections nor improved outcomes in patients with ischemic or hemorrhagic stroke.[50] The ESPIAS study even suggested a nonsignificant increase in mortality in the treatment group. The Preventive Antibacterial Therapy in Acute Ischemic Stroke (PANTHERIS) study demonstrated the efficacy of preventive antiinfective therapy with moxifloxacin.[51] Even though the infection rate was reduced in patients treated with moxifloxacin, survival and neurologic outcomes were not significantly improved compared to placebo group. Minocycline is a tetracycline antibiotic that is being developed as a neuroprotective acute stroke treatment.[52] Whether minocycline will also prevent fever after stroke is unknown.

Antipyretics: The most commonly used antipyretic is acetaminophen, although aspirin, ibuprofen, or indomethacin have also been tried when the risk of bleeding is considered low. In a study of patients admitted within 12 hours of an acute ischemic stroke, body temperature was monitored for 48 hours.[53] When temperature exceeded 37.5°C, treatment was started with either aspirin 900 mg or acetaminophen 1000mg. Patients who remained febrile after 6 hours were treated with acetaminophen up to four times/day. Although acetaminophen was more effective in reducing temperature than was aspirin at one hour, both drugs were similarly ineffective, with normothermia achieved in only 37–38% of patients at 3 hours. Several small clinical trials have tested acetaminophen as a treatment for acute stroke, finding a consistent reduction in temperature of only about 0.25°C but no effect on clinical outcome.[54–56]

In the Paracetamol (acetaminophen) in Stroke (PAIS) trial, 1400 patients were randomly assigned to either acetaminophen 1 g 6 times/day or placebo; both were administered routinely to patients within 12 hours of stroke onset and continued for 3 days.[57] No benefit on stroke outcome was detected, and the average temperature lowering was a modest 0.25°C. In the group of patients with elevated baseline temperature (37–39°C), treatment with acetaminophen appeared to improve outcome in post hoc analysis. This study demonstrates that doses of acetaminophen in excess of the maximum recommended daily dose (i.e., 4 g/day at that time), do not achieve greater temperature lowering than that of the 3900-mg/day dose in other studies. The aforementioned study left open the possibility that acetaminophen could improve outcome in patients with stroke and fever without dramatically lowering body temperature.

A recent study showed that routine use of acetaminophen 1 g 3 times/day can significantly increase blood pressure in patients with coronary artery disease.[58] This finding further adds

to the caution that must be taken in using this agent in patients with stroke, where blood pressure lowering is needed to prevent recurrence.[38]

Recently, acetaminophen became available for administration by the intravenous route. The place of intravenous acetaminophen is limited to reducing pain and fever in clinical situations where oral or rectal acetaminophen cannot be administered. However, to the best of our knowledge, no published data are available on the use of intravenous acetaminophen for fever reduction after stroke.

With regard to other antipyretic agents, one group investigated whether ibuprofen led to a reduction of body temperature in patients with acute ischemic stroke, even when they had no fever.[54] They found that ibuprofen had no statistically significant effect on body temperature during the entire study period.

Conclusion

The American Heart Association-American Stroke Association guidelines for the treatment of fever in the acute stroke period recommend that elevated body temperature should be lowered. The guidelines emphasize, however, that no data are available demonstrating that lowering body temperature in either febrile or afebrile patients improves neurologic outcome after stroke, and the temperature goals are unknown. Treatment with antipyretics should be considered very carefully, since fever lowering may prolong the course of infection in humans. Preventive administration of antipyretics may also mask infections and lead to delayed treatment with antibiotics in cases when they are indicated.

Appreciable temperature reduction can be reliably achieved only by nonpharmacologic means, but physical cooling can provoke shivering and vasoconstriction. No specific recommendations can be made regarding the use of nonpharmacologic approaches to cooling for the treatment of fever, but these appear the most promising and should be pursued.

We believe that the evidence supporting the use of oral antipyretics to lower body temperature is inadequate. Acetaminophen, in the doses recommended for fever treatment, has limited efficacy in critically ill patients and can quickly exceed the maximum daily dose, especially the new maximum of 3 g/day, putting the patient at risk of hepatic toxicity.

The clinical benefits of lowering temperature have yet to be established in large patient samples. Additional study is needed to determine if fever is a contributor to or only a marker of poor outcome and, more important, to define optimal treatment.

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