Relationship between body temperature and neurological outcome in patients with acute brain injury: systematic review of clinical evidence

Pegoli M.¹, Sergi P.², Zanello M.^{1,3}

¹ IRCCS delle scienze neurologiche - Ospedale Bellaria, Anaesthesiology & Intensive Care, Bologna, Italy,

² Policlinico Gemelli, Anaesthesiology & Intensive Care, Roma, Italy,

³ Alma Mater Studiorum - University of Bologna, Bologna, Italy, Department of Biomedical and NeuroMotor Sciences, Bologna, Italy

Background and Goal of Study

Temperature alterations in neurocritical care setting have striking effect on brain metabolism leading or exacerbating neuronal injury. Fever is common in N-ICU (nearly 70% of patients) and also negatively impact on acute brain injury (ABI) patients outcome in terms of mortality and ICU/hospital length of stay. There are emerging evidence in favor of maintaining normothermia (that include temperature lowering in patients with hyperthermia and fever and rewarming in patients with spontaneous hypothermia) in critically ill patients. However conclusive evidence linking control of temperature to improved outcome is still lacking.

Aim of this literature review is to evaluate the relationship between changes in body temperature in ABI and outcome.

Table 2. Summary of Meta-Analysis Findings: Effect Size, Association, and RR

Outcome Measure	No. of Articles/Hypotheses*	Total N	Zc†	Effect Size‡	RR	Fever/Higher Body Temperature Associated Significantly With
Mortality	24/24	10 460	6.31	0.46	1.5	Death
GOS	9/11	1625	3.66	0.26	1.3	Neurological deficit/death
BI	8/10	2841	4.85	0.65	1.9	More dependence
mRS	5/5	1423	-27.6	0.89	2.2	Lower functioning
CSS	5/8	910	6.09	0.35	1.4	Greater severity
ICU LOS	6/6	5418	48.48	1.66	2.8	Longer ICU stay
Hospital LOS	3/3	4468	39.55	1.53	3.2	Longer hospital stay

*Sum does not equal total articles because some articles evaluated more than one outcome measure.

†Zc is Winer's Zc for the Rankin scale and the 2 LOS measures, Stouffer's Zc for all others. For the mRS, Winer's Zc is negative because mRS scores increase as outcomes worsen, whereas the opposite occurs with the other ordinal scales.

‡Cohen's d corrected for sample size.

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Table 1 Clinical evidence for targeted temperature management (TTM) in different types of acute brain injury

Pathology	Recommendation	Level of evidence [reference]
Cardiac arrest	Strong evidence in favor of improved survival and functional outcomes for cooling in patients with out-of-hospital cardiac arrest, although recent evidence suggests no difference in benefit between cooling to 33 or 36 °C. There is no obvious benefit of prehospital cooling on immediate or long-term outcomes	Level I [28] [30•] [11**]
Traumatic brain injury	No role for early TTM in traumatic brain injury in adults or children. Recent data suggest worsened functional outcomes and mortality rates when hypothermia is used as a second-tier treatment for intracranial hypertension. For refractory intracranial hypertension in traumatic brain injury, however, the evidence is less clear and TTM is used in many centers	Level I [31] [32] [35**]
Acute ischemic stroke	Some encouraging evidence, albeit mainly from small underpowered feasibility trials. High rates of fatal herniation observed during rewarming emphasizes the importance of slow rewarming. Data from ongoing Phase II/III trials are awaited	Level II [37] [38] [40]
Intracerebral hemorrhage	A treatment option for management of intracranial hypertension and reducing symptomatic mass effect in the presence of peri-hematoma edema. TTM can also be used for refractory pyrexia	Level III [42]
Subarachnoid hemorrhage	Currently only indicated for managing refractory intracranial hypertension and fever, but it may also reduce the incidence of delayed cerebral ischemia	Level III [45-49]
Neonatal hypoxic-ischemic encephalopathy	Babies born at term (or near term) with moderate or severe hypoxic-ischemic encephalopathy should be treated with TTM within 6 h of delivery, maintained over 72 h with slow rewarming over ≥4 h	Level I [52]

Materials and Methods

A literature search of 2 medical data base was accomplished: PubMed Medline. Only complete studies (no abstracts), published in English in peer-reviewed journals were included. Two authors (M.P and P.S) independently screened and assessed titles, abstracts, and the full-text papers, using inclusion and exclusion criteria. A total of 32401 papers were screened and 32354 were excluded. We present 47 articles into 5 subchapters: mixed acute brain injury (7), brain trauma (6), intracranial hemorrhage (5), subarachnoid hemorrhage (12); ischemic stroke (17).

Results and Discussion

The distinctive feature of this SR of clinical literature – published between March 2006 to October 2016- is to report evidence related to temperature variations in patients with ABI.

ABI: fever correlates with increased inhospital mortality and poor functional outcome increasing brain metabolism and reducing blood flow. Fever increase PIC, decrease CPP and promote secondary brain injury.

Brain trauma: fever in the first 48 hours after trauma did not predict mortality. Both the degree and duration of early post-trauma hyperthermia were strongly related with outcome. A synergic effect on outcome is seen with moderate/severe ICP elevation.

Intracranial hemorrhage: fever determines higher mortality and short and long term poor prognosis. Also subacute fever in association with large volume hematoma is a driver of neurological deterioration.

Subarachnoid hemorrhage: the impact of fever on poor outcome is related to cerebral inflammatory response initiated at the time of aneurysm rupture, increased rate of vasospasm and DIND, increased ICP related to metabolic distress. Fever also consistently correlates with mortality.

Acute ischemic stroke: delayed hyperthermia has a greater adverse association with long-term outcomes and mortality compared with early period after an ischemic stroke. In patients treated with recanalization the role of hyperthermia on outcome is still controversial. Also short term subfebrile temperatures could exacerbate brain damage.

Conclusions

Fever, regardless whether infectious or central, is strongly correlated with poor neurological and functional outcome. Optimal body temperature, how long, the best way (pharmacological vs physical) to maintain it and the optimal method to recognise and treat infections in absence of fever remain still to define. Further studies are needed to confirm characteristics of maintaining normothermia in neurologically injured patients and the impact on outcome.

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