OPEN

Shivering Treatments for Targeted Temperature Management: A Review

Akash Jain, Maria Gray, Stephanie Slisz, Joseph Haymore, Neeraj Badjatia, Erik Kulstad

LITERATURE REVIEW

ABSTRACT

Background: Shivering is common during targeted temperature management, and control of shivering can be challenging if clinicians are not familiar with the available options and recommended approaches.
Purpose: The purpose of this review was to summarize the most relevant literature regarding various treatments available for control of shivering and suggest a recommended approach based on latest data.
Methods: The electronic databases PubMed/MEDLINE and Google Scholar were used to identify studies for the literature review using the following keywords alone or in combination: ''shivering treatment,'' ''therapeutic hypothermia,'' ''core temperature modulation devices,'' and ''targeted temperature management.''
Results: Nonpharmacologic methods were found to have a very low adverse effect profile and ease of use but some limitations in complete control of shivering. Pharmacologic methods can effectively control shivering, but some have adverse effects, such that risks and benefits to the patient have to be balanced.
Conclusion: An approach is provided which suggests that treatment for shivering control in targeted temperature management should be initiated before the onset of therapeutic hypothermia or prior to any attempt at lowering patient core temperature, with medications including acetaminophen, buspirone, and magnesium sulfate, ideally with the addition of skin counterwarming. After that, shivering intervention should be determined with the help of a shivering scale, and stepwise escalation can be implemented that balances shivering treatment with sedation, aiming to provide the most shivering reduction with the least sedating medications and reserving paralytics for the last line of treatment.

Keywords: core temperature modulation devices, normothermia, shivering control in targeted temperature management, shivering control in TTM, shivering scale, shivering treatment, targeted temperature management, therapeutic hypothermia, therapeutic normothermia

Hyperthermia has been associated with worsened outcomes in all forms of acute brain injury.[1,2] Fever, regardless of the cause, has been linked to increases in mortality, disability, and length of stay.[2,3] The term *targeted temperature management* (TTM) refers to any intervention or treatment that intentionally

Questions or comments about this article may be directed to Akash Jain, MBBS, at akashjain2019@gmail.com. Medical Officer, Government of Rajasthan, India.

Maria Gray, MA RN, is Vice President for Clinical Services, Attune Medical, Chicago, IL.

Stephanie Slisz, BSN RN, is Senior Clinical Specialist, Attune Medical, Chicago, IL.

Joseph Haymore, DNP ACNP, is Senior Nurse Practitioner and Advanced Practice Provider Research Director, Neurocritical Care Intensive Care Unit, University of Maryland Medical Center, Baltimore, Maryland.

Neeraj Badjatia, MD, is Professor of Neurology and Vice Chair for Hospital Operations, Department of Neurology, University of Maryland School of Medicine and R Adams Cowley Shock Trauma Center, Baltimore, MD.

Erik Kulstad, MD MS, is Associate Professor, Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX.

E.K., S.S., and M.G. work with a company, Attune Medical, commercializing temperature management technology. For the remaining authors, no conflicts of interest were declared.

DOI: 10.1097/JNN.0000000000000340

targets a patient temperature, including induced hypothermia, controlled normothermia, and fever control.[1] In the neurologically injured patient, TTM can assist in modulating the reperfusion injury by decreasing mitochondrial dysfunction, free radical production, and metabolism.[2] Questions still remain regarding the best approach for using TTM and managing associated adverse effects.

A common adverse effect of TTM is shivering, occurring in up to 40% of patients undergoing TTM.[4] Shivering can cause a significant decrease in brain tissue oxygen tension ($PbtO_2$) causing cerebral metabolic stress, potentially eradicating the benefits of TTM.[1,5,6] Therefore, adherence to standardized protocols for the assessment and treatment of shivering is likely necessary to realize the full benefits of TTM. Implementing a stepwise approach to address shivering that prioritizes the least sedating interventions and standardizes treatment may be beneficial.[7] Clinical assessment of shivering, reflecting the efficacy of the protocol interventions, can be measured through assessment with the Bedside Shivering Assessment Scale (see Table 1).

The purpose of this review was to analyze the available treatments with their limitations for shivering control in TTM. Shivering treatments available for use during the induction and maintenance of TTM include pharmacological and nonpharmacological methods. Both of these categories of treatment can be used with any of the available approaches or devices used to induce and maintain TTM. However, there are typically different degrees of shivering caused by different devices, with core temperature modulation offering less shivering than surface because skin surface receptors are known to play a significant role in the initiation of shivering.[7–9] Hereinafter, we review the various methods of treating shivering and, after that, suggest recommendations based on currently available data and practice from experienced sites.

TABLE 1. Bedside Shiver Assessment Scale

Score	Shivering	Patient Behavior
0	None	No shivering
1	Mild	Shivering localized to the neck/thorax, may be seen only as an artifact on ECG or felt by palpation
2	Moderate	Intermittent involvement of the upper extremities ± thorax
3	Severe	Generalized shivering or sustained upper/lower-extremity shivering

Nonpharmacological Methods

Nonpharmacological methods include active cutaneous counterwarming, body core warming, passive cutaneous warming, and electroacupuncture, but in practice, active cutaneous counterwarming is the most commonly used method.[10] Some researchers have found shivering suppression with focal hand warming; some have found warming the lower face plus inhaled heated/humidified air to be beneficial to suppress shivering.[6] Because shivering is a thermoregulatory reflex triggered by core temperature being lower than the hypothalamic set point, and because mean skin temperature contributes 20% to the control of shivering, the application of forced-air warming may ameliorate shivering. Some areas of the body, such as the hands and face, have a higher concentration of cutaneous temperature sensors, such that warming of those areas may have a greater effect on suppressing shivering, although this regional difference is not consistently reported.[10]

Using a heated forced-air blanket (Bair Hugger; 3M Corporation, Maplewood, Minnesota), Badjatia and coworkers[6] found a 1°C decrease in the shivering threshold with every 4°C increase in mean skin temperature. A prospective study by Badjatia et al[10] found that the addition of a forced-air warming blanket (maximum of 43°C) was effective in restricting the metabolic impact of shivering in the neurologically impaired patient, adding that it is safe, inexpensive, and nonsedating.

Pharmacological Treatments

A wide variety of medications can be used to control shiver. In general, the most commonly used agents belong to the following classes: (*a*) nonnarcotic analgesic/antipyretic, salicylate analgesic/antipyretic, and nonsteroidal anti-inflammatory drugs (NSAIDs); (*b*) agents to induce arterial vasodilation; (*c*) opioid analgesics; (*d*) α-agonists; (*e*) anesthetics and sedatives; (*f*) serotonin (5-hydroxytryptamine [5-HT]) agonists; (*g*) N-Methyl-D-aspartate (NMDA) antagonists; and (*h*) neuromuscular blockade (NMB) agents. Essentially, every class of drug is associated with some adverse effect(s) that may limit its usefulness. Pharmacological methods used during shivering management require adequate attention to the degrees of sedation, hemodynamic effects, and NMB. Choi and coworkers[7] have shown that, by using a stepwise, protocol-driven approach, patients undergoing temperature modulation can be effectively treated for shivering without oversedation and paralysis. Moreover, the use of different pharmacologic options may offer synergistic benefits, as well as potential synergistic disadvantages.

Antipyretics

Antipyretic agents, including acetaminophen, aspirin, and NSAIDs, are believed to block endogenous pyrogens by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain, the substances responsible for elevating the hypothalamic set point—leading to peripheral vasodilation and sweating. Antipyretic agents may have limited effectiveness in brain-injured patients if the thermoregulatory mechanisms are impaired. In patients with hemorrhagic or ischemic stroke, Kasner et al[11] observed a difference of 0.2°C in body temperature with the use of acetaminophen (approximately 4 g/d) in comparison with placebo, but this was not statistically significant.

Magnesium

Administration of intravenous magnesium sulfate (serum level target, 3–4 mg/dL) increases the cooling rate and comfort when using a surface cooling technique by reducing smooth muscle tone and subsequent vasodilation, leading to a reduced incidence of shivering.[7,10,12] Magnesium is often used in protocols to stop shivering when it occurs. Magnesium sulfate may also provide additional benefits in patients with brain injury through its apparent neuroprotective property as an NMDA antagonist.[13] The magnitude of the effect of shivering reduction may be less than other pharmacologic agents, but the low adverse effect profile of magnesium provides little disincentive for its use.[13]

Opioid Analgesics

Opioid analgesics are widely used to reduce shivering in TTM. Morphine, fentanyl, alfentanil, and meperidine are most commonly used for shivering, with meperidine as perhaps the most effective.[14,15] Meperidine decreases the shivering threshold almost twice as much as the vasoconstriction threshold; this is in distinct contrast to other analgesic and sedative drugs, including propofol, dexmedetomidine, and midazolam. Shivering control with butorphanol and tramadol has also been shown, but respiratory depression with butorphanol, and dyspnea, dizziness, somnolence, and flushing with tramadol are possible adverse effects in patients susceptible to them (primarily nonintubated patients).[16] Controversy exists regarding the potential for meperidine to lower the seizure threshold, but definitive quantification of this risk is limited.[14,17,18] A combination of meperidine and buspirone has been shown to decrease the shivering threshold, but this combination has been suggested by some to potentially increase the risk of seizures with renal impairment. Meperidine has also shown a synergistic reduction in the shiver threshold when used with skin counterwarming.[19]

α-Agonists

Dexmedetomidine can manage shivering during TTM; however, it can be associated with bradycardia and hypotension.[7,18] Dexmedetomidine has been shown to successfully reduce the shivering threshold in healthy volunteers.[20] In addition, meperidine can be used with buspirone and dexmedetomidine to synergistically lower the shivering threshold. According to Alfonsi and coworkers, nefopam and clonidine reduce the shivering threshold by 0.7°C (to 35.7°C); however, nefopam has been reported to induce seizures and anaphylactic reactions, and its availability is primarily in European countries.[21] A combination of buspirone and dexmedetomidine has been shown to additively reduce the shivering threshold by 2.5°C (to 34.1°C) with only minimal sedation. Buspirone is available only for enteral administration and therefore, in comatose patients, must be administered via nasogastric tube, orogastric tube, or rectally.[22]

Anesthetics and Sedatives

Midazolam and propofol are the most widely used sedative agents. Chamorro and coworkers found that midazolam has a high sedative effect and a low risk of hypotension.[23] The use of benzodiazepines (midazolam) for sedation is associated with a significant increase in the development of delirium.[24] Propofol has been compared with thiopental and isoflurane; patients who received propofol in general experienced less shivering as compared with those who received thiopental and thiopental with isoflurane.[25] Although propofol has been shown to control shivering, it has the risk of hypotension and propofol infusion syndrome with higher doses and prolonged use.[16,21,26]

Serotonin (5-HT) Agonists/Antagonists

Multiple 5-HT agonists and antagonists have shown efficacy on reducing shivering, including buspirone, tramadol, and ondansetron, among others. A single large dose of buspirone (60 mg) has a modest reduction in the shiver threshold by up to 0.7°C.[15] However, buspirone (30 mg) used in combination with low-dose meperidine has a similar reduction on the shiver threshold (2.3°C) as a large dose of meperidine alone. Tramadol is a partial 5-HT antagonist that has a modest effect on reducing the shiver threshold (0.2°C) that was not linked to the μ-opioid activity of tramadol.[16]

NMDA Antagonists

In addition to the NMDA effects of magnesium sulfate discussed previously, ketamine has also been investigated for shiver. Boluses of low-dose ketamine (0.5–0.75 mg/kg) have shown efficacy in shiver prevention and treatment. However, there is a paucity of

TABLE 2. Suggested Antishivering Protocol

When to Initiate	Typical BSAS Score at Initiation	Intervention	Dose	Goal of Intervention
Before starting temperature management, administer all 3 medications in this category.	0	Acetaminophen	650–1000 mg PO/PR/NGT mg Q 4–6 h	Prevention of shivering
		Buspirone	30 mg PO/PR/NGT Q 8	
		Magnesium sulfate	0.5–1 g/h IV or 4g bolus; goal serum magnesium level of 3–4 mg/dL	
		Skin counterwarming	43°C/MAX Temp	
When shivering is localized to the neck/thorax; may be seen only as an artifact on ECG or felt by palpation	1	Dexmedetomidine or opioid	Dexmedetomidine 0.2–1.5 mcg/kg/h Fentanyl starting dose, 25 mcg/h Meperidine 50–100 mg IM or IV	Mild sedation
When shivering includes intermittent involvement of the upper extremities ± thorax	2	Dexmedetomidine and opioid	As above Consider continuous IV infusion of fentanyl 0.25–2 mcg/kg/h	Moderate sedation
When generalized shivering or sustained upper/lower-extremity shivering is present	3	Propofol	25–75 mcg/kg/min	Deep sedation
When generalized shivering or sustained upper/lower-extremity shivering is present despite use of medications at preceding levels	3	Rocuronium bolus or cisatracurium infusion or vecuronium bolus or pancuronium bolus	0.3–0.9 mg/kg 1–2 mcg/kg/min 0.08 – 0.1 mg/kg IV 0.04 – 0.1 mg/kg IV	Neuromuscular blockade, last resort after inability to control shivering despite all other medications

Note. If shivering worsens, add sequential interventions as appropriate after increasing numerical score of the BSAS, but continue all lower level interventions. Additional medications in the above classes may also be considered, such as ondansetron, tramadol, ketamine, etc.

literature discussing the use of ketamine as a continuous infusion. Although ketamine is effective, it is not superior to meperidine or dexmedetomidine.[27,28]

Neuromuscular Blockade

Many TTM protocols suggest the use of an NMB to control shivering if all other approaches fail. A study conducted by Dupuis et al[29] found vecuronium better than pancuronium for reduction of shivering because vecuronium was not shown to increase myocardial work and was associated with fewer complications. Neuromuscular blocking agents are associated with prolonged obscuration of the neurological examination, prolonged length of stay in the neurointensive care unit, and prolonged mechanical ventilation, increasing the risk of developing ventilator-associated pneumonia.[30] The use of TTM may interfere with clinical monitoring of NMB because hypothermia alters the normal peripheral response to a train-of-four assessment. Decreased responsiveness to monitoring and prolonged duration of effect with the NMB agents during hypothermia increase the risks of long-term adverse effects seen with NMBs.

Recommendations

Targeted temperature management is associated with shivering. Treatment methods of shivering include both nonpharmacologic and pharmacologic agents. Best practices include initiating treatment prophylactically at the initiation of TTM. Shivering interventions should be assessed with the help of a shivering scale. We recommend a tiered protocol to prevent and treat shiver. Patients who are started on TTM should have an appropriate antipyretic agent (acetaminophen or NSAID) given every 4 to 6 hours around the clock. Standing doses of buspirone (30 mg) should be given

every 8 hours. Intravenous magnesium sulfate should be given either as a continuous infusion or in boluses to achieve and maintain a serum magnesium level of 3 to 4 mg/dL. Last, skin counterwarming using a heated (maximum of 43°C) forced-air blanket should be initiated. If the patient develops shiver, the interventions should be chosen based on the degree of shivering (ie, mild, moderate, severe) (see Table 2).

References

1. Badjatia N. Hyperthermia and fever control in brain injury. *Crit Care Med*. 2009;37(7 suppl):S250-7–S250-7.
2. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008;371(9628):1955–1969.
3. Rockett H, Thompson HJ, Blissitt PA. Fever management practices of neuroscience nurses: what has changed? *J Neurosci Nurs*. 2015;47(2):66–75.
4. Badjatia N. Therapeutic temperature modulation in neurocritical care. *Curr Neurol Neurosci Rep*. 2006;6(6):509–517.
5. Presciutti M, Bader MK, Hepburn M. Shivering management during therapeutic temperature modulation: nurses' perspective. *Crit Care Nurse*. 2012;32(1):33–42.
6. Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke*. 2008;39(12): 3242–3247.
7. Choi HA, Ko SB, Presciutti M, et al. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. *Neurocrit Care*. 2011;14(3):389–394.
8. Hegazy AF, Lapierre DM, Butler R, Althenayan E. Temperature control in critically ill patients with a novel esophageal cooling device: a case series. *BMC Anesthesiol*. 2015;15:152.
9. van Zanten AR, Polderman KH. Blowing hot and cold? Skin counter warming to prevent shivering during therapeutic cooling. *Crit Care Med*. 2009;37(6):2106–2108.
10. Badjatia N, Strongilis E, Prescutti M, et al. Metabolic benefits of surface counter warming during therapeutic temperature modulation. *Crit Care Med*. 2009;37(6):1893–1897.
11. Kasner SE, Wein T, Piriyawat P, et al. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke*. 2002;33(1):130–134.
12. Weant KA, Martin JE, Humphries RL, Cook AM. Pharmacologic options for reducing the shivering response to therapeutic hypothermia. *Pharmacotherapy*. 2010;30(8):830–841.
13. Boet R, Chan MT, Poon WS, Wong GK, Wong HT, Gin T. Intravenous magnesium sulfate to improve outcome after aneurysmal subarachnoid hemorrhage: interim report from a pilot study. *Acta Neurochir Suppl*. 2005;95:263–264.
14. Kurz, A, Ikeda T, Sessler DI, et al. Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. *Anesthesiology*. 1997;86(5):1046–1054.
15. Ikeda T, Kurz A, Sessler DI, et al. The effect of opioids on thermoregulatory responses in humans and the special antishivering action of meperidine. *Ann N Y Acad Sci*. 1997; 813:792–798.
16. De Witte JL, Kim JS, Sessler DI, Bastanmehr H, Bjorksten AR. Tramadol reduces the sweating, vasoconstriction, and shivering thresholds. *Anesth Analg*. 1998;87(1):173–179.
17. Takada K, Clark DJ, Davies MF, et al. Meperidine exerts agonist activity at the alpha(2B)-adrenoceptor subtype. *Anesthesiology*. 2002;96(6):1420–1426.
18. Doufas AG, Lin CM, Suleman MI, et al. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke*. 2003;34(5):1218–1223.
19. Kimberger O, Ali SZ, Markstaller M, et al. Meperidine and skin surface warming additively reduce the shivering threshold: a volunteer study. *Crit Care*. 2007;11(1):R29.
20. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. *Anesthesiology*. 1997;87(4):835–841.
21. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009; 37(7 suppl):S186–S202.
22. Honasoge A, Parker B, Wesselhoff K, Lyons N, Kulstad E, et al. First use of a new device for administration of buspirone and acetaminophen to suppress shivering during therapeutic hypothermia. *Ther Hypothermia Temp Manag*. 2016;6(1):48–51.
23. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101–1120.
24. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013;41(9 suppl 1): S30–S38.
25. Singh P, Harwood R, Cartwright DP, Crossley AW. A comparison of thiopentone and propofol with respect to the incidence of postoperative shivering. *Anaesthesia*. 1994; 49(11):996–998.
26. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C. Propofol linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology*. 1995; 82(5):1169–1180.
27. Eydi M, Golzari SE, Aghamohammadi D, Kolahdouzan K, Safari S, Ostadi Z. Postoperative management of shivering: a comparison of pethidine vs. ketamine. *Anesth Pain Med*. 2014; 4(2):e15499.
28. Reddy AV, Kumer KK. Dexmedetomidine infusion versus intravenous low-dose ketamine injection in preventing intraoperative shivering during spinal anesthesia: a comparative study. *J Med Sc Clin Res*. 2017;5(8):26121–26128.
29. Dupuis JY, Nathan HJ, DeLima L, Wynands JE, Russell GN, Bourke M. Pancuronium or vecuronium for treatment of shivering after cardiac surgery. *Anesth Analg*. 1994;79(3):472–481.
30. Rello, J, Diaz E, Roque M, Vallés J. Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med*. 1999;159(6):1742–1746.