Sedative Choice: The Chilling Confounder to Targeted Temperature Management

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Abstract

Targeted temperature management (TTM) is a technique used in adults who lack a meaningful response after the return of spontaneous circulation following cardiac arrest (CA). The implementation of TTM is believed to improve neurological outcomes by decreasing cerebral metabolism, reducing apoptosis, and lowering oxygen demand. While this technique is recommended as a part of advanced cardiovascular life support (ACLS), there is a lack of consistency regarding drug choice and depth of sedation in TTM. In this report, the authors provide a review of the myriad of regimens outlined in research protocols and current guidelines to stimulate discussion and promote further studies pertaining to sedation strategies in TTM. Through this call to action, the ultimate goal is to develop a uniform approach to bedside practice.

Keywords: analgesics, physician prescribing, medication safety, CPR, critical care

TTM is a standard-of-care in advanced cardiovascular life support algorithms for comatose adults after cardiac arrest to improve neurologic outcomes. In this commentary, we caution clinicians against accepting the apparent clinical equipoise for targeted temperature management (TTM) until the confounding role of sedative pharmacotherapy is thoroughly evaluated. Lascarrou, et al. and Dankiewicz, et al. recently published results adding to a series of studies observing no benefit in the key outcomes of mortality, length of stay, and duration of mechanical ventilation among patients undergoing TTM.[1-3] While these trials highlight the deleterious effects of hyperthermia following cardiac arrest, we believe that inconsistency in trial design regarding the management of analgesia, sedation, and neuromuscular blockade (NMB) precludes definitive practice changes. According to the CAPITAL CHILL trial, an analgesic, sedative, and paralytic is the current standard of care. However, this is misleading as the standard of care has not been clearly outlined by any societal guidelines that currently exist.[4] It has not been commonplace for trial groups to report sedation management strategies such as target sedation goals, agent selection, and titration parameters. With no guideline recommendations specific to TTM, there is substantial discordance among randomized controlled trials and guideline statements of various societies. We contend that two key methodologic omissions prohibit definitive conclusions given what is generally known about best practices for sedation strategies in ICU patients:[1]

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1. Sedative administration strategies were not reported in the study findings
2. Sedative strategies targeted for TTM vs. shivering were not differentiated

Overall, there is a lack of transparency and consistency in methodology regarding type and depth of sedation for TTM. Lack of specification for sedative agent choice creates a milieu of problems. For example, midazolam and propofol are considered functionally interchangeable in the Lascarrou, et al. and Dankiewicz, et al studies, despite vast amounts of evidence demonstrating worse outcomes with benzodiazepines.[2,3] Sedation with propofol and remifentanil have been consistently shown to have faster offset that is associated with earlier awakening and more ventilator-free days than patients who received midazolam and fentanyl. This raises the question of whether the observed neurologic outcomes in these studies was secondary to injury following cardiac arrest or residual effects of medications?[5,6] Additionally, depth of sedation achieved is an independent predictor of patient outcomes but was not reported by Lascarrou, et al. and Dankiewicz, et al.,[2,3] in either *a priori* design or in their findings. This is a notable omission because light vs. deep sedation has been shown to have an impact on patient outcomes and represents a confounder that is not considered or controlled for.

Further, the inconsistencies in clarifying the use of sedation for TTM compared to shivering introduces confounders that preclude the definitive role of TTM for neurologic outcomes. NMB may also be implemented during TTM to reduce shivering, but this practice requires deep sedation (and that may also significantly impact prognostication).[7] Combining patients who received sustained NMB at initiation of TTM (and the associated deep levels of sedation) and those in which NMB administration was reserved (and possibly not administered) for refractory

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shivering once again emphasizes this point. With the lack of clarity regarding implementation strategies, identifying current literature regarding sedation in TTM is essential to guiding practice. Key components of treatment protocols and relevant patient level description of use in various trials have been summarized in **Table 1**.

Moreover, the impact of TTM on drug metabolism has not been rigorously evaluated in regard to clinical outcomes and neurologic prognosis in this patient population, despite pharmacodynamic and pharmacokinetic characteristics being dependent upon body temperature. While sedation is limited in duration during TTM, the role pharmacotherapy plays in prognostication soon after rewarming is an outcome that should be emphasized.[7] In the post-cardiac arrest care guidelines, which identify sedation as a confounder to prognostication using clinical examination, how to account for residual drug metabolites during neurologic evaluation in the clinical setting has not been addressed.[1]

Overall, we caution that it is premature to discount the effects of temperature control on neurological improvement without first considering the confounding impact of pharmacotherapy on patient outcomes. In light of this, future studies should aim to clearly define sedation strategies in TTM in hopes to standardize treatment.

The opinions expressed in this paper are those of the authors.

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Table 1. Key factors from published treatment protocols and randomized trials on analgesia, sedation, and neuromuscular blockade during temperature control after cardiac arrest

Reference	Analgesia	Sedation	Neuromuscular blockade
Bernard, et al. 2002[8]	Not mentioned.	Sedation and paralysis at induction with small doses of midazolam and vecuronium. Continued boluses given as needed to prevent shivering	
Holzer, et al. 2002[9]	Fentanyl (0.002mg/kg/h initially), and doses were adjusted as needed for 32 hours	Sedation induced by the IV administration of midazolam (0.125mg/kg of body weight per hour initially) and doses were adjusted as needed for 32 hours	To prevent shivering, paralysis was induced by the IV administration of pancuronium (0.1mg/kg) every 2 hours for 32 hours
Nielsen, et al. 2013[10]	All patients received fentanyl	Propofol or midazolam continuous infusion used for duration of TTM Sedation based on hemodynamic status Sedation maintained for 36 hours. After this period, mandatory sedation was discontinued or tapered No detailed data on dose and type of sedation	No detailed data on the use of NMB agents Paralysis with NMB agents when necessary, to reduce shivering
Kirkegaard, et al. 2017[11]	Majority of patients were sedated with propofol and remifentanil Midazolam and fentanyl were used in a minority of patients Sedation was used until rewarming was complete Sedation based on hemodynamic status		Infusion of NMB agents were used Cisatracurium continuous infusion utilized if needed during induction; subsequent boluses as needed for shivering Only 61 out of 351 patients received cisatracurium

Lascarrou, et al. 2019[2]	In the moderate therapeutic hypothermia group, all patients received sedation with midazolam or propofol combined with fentanyl or sufentanil Sedation was provided according to the standard protocol in each center, with dosage adjustment to obtain Richmond Agitation- Sedation Scale score of -5 During rewarming, sedation was tapered when the body temperature rose above 36° C Sedation was given routinely only during the first 12 hours after randomization	Trial protocol included standardization of neuromuscular blockade Persistent shivering was treated according to a previously published three-step protocol. Step 1: single IV bolus of a hypnotic agent and an opioid, in doses equal to the hourly infusion rates Step 2: IV bolus of a nondepolarizing NMB (10mg cisatracurium) Step 3: Continuous infusion of a nondepolarizing NMB (cisatracurium at an initial dose of 10mg/h) to achieve a BSAS of ≤1. During rewarming, the infusion may be stopped when the core body temperature increases above 35° C
Dankiewicz, et al. 2021[3]	Sedation was mandated during the intervention period of 40 hours for all patients to lessen the difference in sedative amounts between normothermia and hypothermia groups Short-acting drugs or volatile anesthesia recommended for sedation and analgesia The sedative should be titrated to achieve deep sedation (RASS score of -4) For shivering, patients will receive increased sedation with propofol/dexmedetomidine and/or opiate. If hemodynamically unstable, midazolam may be substituted for propofol	Use of NMB agents are recommended to facilitate induction of hypothermia Shivering may be treated with a NMB agent if sedation is inadequate

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May, et al. 2021[4]	Emergency Department Orders: Administer a fentanyl 50 mcg IV bolus, then start fentanyl infusion at 1 mcg/kg/hr Titrate infusion every 15 minutes and minimum MAP of 65 mmHg Fentanyl 25-50 mcg IV bolus PRN Cardiac Intensive Care Unit Orders: Sufentanil infusion 250 mcg IV at a recommended rate of 0.1-0.3 mcg/kg/hr	Emergency Department Orders: Midazolam 1-2 mg IV bolus; repeat every 5 minutes for agitation (max 10 mg/hr) Consider propofol if greater than 10 mg/hr required for sedation Propofol 10-20 mg IV bolus, then start propofol infusion at 0.3 mg/kg/hr Titrate infusion every 5 minutes to Riker score and minimum MAP of 65 mmHg (max 3 mg/kg/hr) Propofol 10-20 mg IV bolus PRN for agitation Cardiac Intensive Care Unit Orders: Propofol 10-20 mg IV bolus recommended, then start propofol infusion at 0.3 mg/kg/hr	Paralysis only to suppress shivering Emergency Department Orders: Rocuronium recommended initial dose 0.6 mg/kg over 5-15 seconds (max 50 mg) Cardiac Intensive Care Unit Orders: Cisatracurium bolus 0.1 mg/kg IV, then recommended infusion 0.5-2 mcg/kg/min Aim to maintain train of four (TOF) at 2:4 to control shivering Do not titrate NMB when TOF is more than 2:4 if Bedside Shivering Assessment Scare (BSAS) is 1 or less and temperature is easily controlled; titrate NMB if TOF is more than 2:4 and BSAS is more than 1 Assess BSAS and TOF hourly If unable to obtain accurate TOF, infuse sedation, analgesia, and NMB agents at minimal rates; increase only if patient is shivering and BSAS is greater than 1