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Supplement 8. Determination of Brain Death/Death by Neurologic Criteria After Treatment With Targeted Temperature Management

This supplementary material has been provided by the authors to give readers additional information about their work.

Determination of Brain Death/Death by Neurologic Criteria After Treatment With Targeted Temperature Management

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Abstract

Introduction Targeted temperature management (TTM) is used for neuroprotection in a number of disease states. Unfortunately, use of TTM to protect the brain does not always prevent progression to cardiopulmonary death or brain death/death by neurologic criteria (BD/DNC). Determination of BD/DNC can be challenging after TTM because it can lead to blunting of brainstem reflexes, particularly in the setting of sedatives or narcotics.

Methods We conducted a review of the literature and formulated recommendations with an expert panel on determination of BD/DNC in persons who were treated with TTM.

Results and Conclusions There have been two reported cases in which BD/DNC was falsely declared in persons treated with TTM. We provide recommendations and suggestions to avoid this and ensure that all determinations of BD/DNC after TTM are performed accurately.

Introduction

Targeted temperature management (TTM) has neuroprotective effects due to reduction in brain ischemia, brain metabolism, intracranial pressure, brain tissue and systemic inflammatory responses; initiation of brain cell apoptosis; and production of free radicals.[1] Because of this, two trials were conducted to investigate the effects of cooling after cardiac arrest. These trials, which were published in 2002, demonstrated improved morbidity and mortality in persons who are cooled after out-of-hospital cardiac arrest.[2,3] A subsequent trial demonstrated that TTM targeting 36°C was noninferior to TTM targeting 33°C.[4] Based on these results, TTM is routinely initiated after cardiac arrest, though the target temperature varies. Additionally, use of TTM in the setting of neurologic injury has since expanded to a variety of different patient populations including those with traumatic brain injury, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and status epilepticus.[5]

Unfortunately, use of TTM to protect the brain does not always prevent mortality. In-hospital death after cardiac arrest has been reported to occur in about 50% of persons due to withdrawal of life-sustaining therapy, cardiopulmonary arrest, or anoxic brain injury leading to progressive cerebral edema, intracranial hypertension and herniation resulting in brain death/death by neurologic criteria (BD/DNC).[6-13] Risk factors for progression to BD/DNC in this population include female gender, young age,

unshockable arrest rhythm, neurologic etiology for arrest and long arrest time (return of spontaneous circulation after more than 30 minutes).[7,10]

Methods

Authors conducted the initial literature searches of the Cochrane, Embase and MEDLINE databases for the time period between January 1, 1992 and July 2017. Subsequent searches were performed to capture relevant articles between July 2017 and April 2020. Because of the significant lack of data from randomized controlled trials or large studies, GRADE evaluation of the evidence was not performed. However, evidence was reviewed by a multidisciplinary group of clinicians (see supplementary material) and recommendations were generated according to the following criteria. Strong recommendations ("It is recommended that") were based on expert consensus that clinicians should follow the recommendation unless a clear and compelling rationale for an alternative approach was present, and where actions could be adopted as policy. Even though most evidence in this area is limited and of low-quality, strong recommendations were made as a precautionary, conservative approach, to prevent premature or erroneous determinations of death (false positives). Conditional or weak recommendations ("It is suggested that") were generated when there were potentially different options and the best action may differ depending on circumstances, patients, resources or societal values, or where there is a need for further evidence or discussion among clinicians and stakeholders. In cases where there was insufficient evidence and the balance of benefits versus harms was neutral, no recommendations were made.

Determination of BD/DNC after TTM

It can be challenging to identify BD/DNC after treatment with TTM because cooling can temporarily blunt brainstem reflexes.[14,15] This effect is particularly pronounced in persons treated with sedation prior to, or concurrent with, use of TTM, due to altered pharmacokinetics and pharmacodynamics resulting in delay of drug elimination.[9,16-21]

Despite this, there is no standard on how long it is necessary to wait after treatment with TTM before BD/DNC can be determined.[17,18,22,23] While some protocols merely note that it is necessary to ensure a person is "not hypothermic" when conducting an evaluation for determination of BD/DNC, others provide discrete temperature recommendations ranging from 32˚C to 36˚C, but do not indicate the amount of time a person must be at this temperature before the exam can be conducted.[14,16-18,22-27] In some cases, protocols indicate that BD/DNC can be declared in persons who are actively being cooled,[16] but in other cases, it is necessary to wait at least 24 hours, if not longer, after rewarming to perform a BD/DNC examination.[20,22,28,29] The exact time at which prior use of sedation and hypothermia no longer confounds the clinical evaluation is unclear,[13,19-21,28,30] but some advocate waiting days to perform a BD/DNC evaluation on a person who was on sedation prior to or during therapeutic hypothermia because it can take several days for drug levels to return to prehypothermia levels and several more days for drugs to be eliminated altogether.[21]

Recovery after Premature Determination of BD/DNC in Persons Treated with TTM

Two case studies on recovery of neurologic function following premature declaration of BD/DNC after TTM have generated extensive discussion in literature.[13,20,21,28,30-33]. In the first case, a 10-month-old boy was cooled after a cardiac arrest and declared brain dead 10 hours after being rewarmed, then

subsequently began breathing again. He was cooled to 32-33˚C for 24 hours post-arrest then rewarmed over 8 hours to 36-37˚C. During this time, he was on a midazolam drip at 2ug/kg/min and was started on phenobarbital. His phenobarbital level 37 hours after the event was 104 μmol/L (therapeutic range 65-170 μmol/L). A computed tomogram of the head 38 hours after the event showed "moderate cerebral edema," per report. A clinical evaluation and apnea test performed 42 hours post-arrest (10 hours after rewarming, 6 hours after discontinuation of the midazolam drip) was consistent with BD/DNC. However, 15 hours later (57 hours after the arrest, 25 hours after rewarming, 21 hours after discontinuation of the midazolam drip), hiccups, which led to some tidal ventilation, were noted. An electroencephalogram was performed and it showed diffuse slowing, but not electrocerebral silence. A nuclear study showed cerebral blood flow. A clinical examination 86 hours after the arrest showed no evidence of brain function, but breathing was noted during apnea testing. Ultimately, treatment was withdrawn and cardiopulmonary death was declared.[31]

In the second case, a 55-year-old man was cooled after a cardiac arrest and declared brain dead 22 hours after being rewarmed, then regained a corneal and cough reflex and began to breathe spontaneously. A computed tomogram 7 hours post-arrest showed an "indistinct gray matter-white matter junction as well as effacement of the sulci and ventricles concerning for diffuse cerebral edema without signs of cerebral herniation," per report. He was initially hypothermic to 35.2˚C, but when he became febrile, TTM was initiated 16 hours post-arrest for a target temperature of < 34˚C. He reached a nadir of 33˚C 48 hours post-arrest, then rewarming began at hour 50, and his temperature was 36.5˚C by hour 56. To control shivering, he was sedated on propofol and fentanyl from hour 14-50. There was no evidence of brain function on clinical examinations performed at 72 hours post-arrest (16 hours post-rewarming and 22 hours after discontinuation of propofol and fentanyl) and 78 hours post-arrest (22 hours post-rewarming and 28 hours after discontinuation of propofol and fentanyl). He did not breathe on an apnea test performed 78 hours post-arrest (22 hours post-rewarming and 28 hours after discontinuation of propofol and fentanyl), and he was declared brain dead at this time. He was taken to the operating room for organ procurement 98 hours post-arrest (42 hours post-rewarming and 48 hours after discontinuation of propofol and fentanyl), and before the procedure, he was found to be breathing spontaneously and to have a cough and corneal reflex. At 106 hours post-arrest, an electroencephalogram showed no electrical activity, despite the fact that he still had a cough and corneal reflex and was taking spontaneous respirations. A subsequent clinical examination 145 hours post-arrest showed loss of all brainstem reflexes. Somatosensory-evoked potentials performed 171 hours post-arrest showed absent N20 responses and a nuclear blood flow study 200 hours post-arrest showed no brain blood flow. Treatment was withdrawn 202 hours post-arrest and death was declared by cardiopulmonary criteria.[30]

Commentary on False Declaration of BD/DNC after TTM

A number of clinicians commented in the literature on what can be learned from these two cases.[13,20,21,33] In both cases, BD/DNC was declared less than 24 hours after rewarming.[30,31] Commentators noted that it is necessary to delay an evaluation for BD/DNC at least 24 hours after rewarming, but that there is no evidence for a specific amount of time to wait before determining a clinical state is irreversible after TTM, and that waiting longer is better.[13,20,21] Secondly, both persons were also on sedation while being cooled, and metabolism of sedatives and narcotics can be slowed at lower temperatures.[30,31,33,34] The half-life of midazolam is 3 hours,[35] so even if the effects of hypothermia

on drug metabolism were ignored in the first case, the BD/DNC determination was performed before even 3 half-lives passed.[31] And in the second case, although over 7 half-lives of fentanyl and 4 half-lives of propofol passed prior to the evaluation for BD/DNC, these drugs were likely still in the patient's system at the time of the evaluation given that clearance of both fentanyl and propofol is significantly prolonged in hypothermia compared with normothermia.[30,34-36] One commentator noted that if the patient had been admitted to a hospital in Germany, it would be necessary to wait 48 hours after fentanyl was stopped or until a serum level demonstrated that sedation was out of his system.[20] It is also notable that the computed tomogram prior to determination of BD/DNC did not show evidence of cerebral herniation in either case.[13,30,31] Lastly, one commentator mentioned that an assessment of brain blood flow is always helpful if there is uncertainty about potential confounders when conducting an assessment for BD/DNC.[13] As is evidenced by the second case, and has been pointed out in the literature previously, use of an electroencephalogram in this setting can be misleading as hypothermia may cause an electroencephalogram to show electrocerebral silence despite clinical evidence of brain function.[30,37,38] In contrast, to our knowledge, transient reversible absence of brain blood flow on an angiogram, nuclear study or ultrasound during hypothermia has not been reported. In fact, a study of cerebral blood flow post-cardiac arrest in 53 persons who were cooled to 33˚C for 24 hours demonstrated that mean blood flow was 559 ± 240 ml/min in the 48 hours post-arrest.[39] Animal studies have also demonstrated that circulation in cerebral microvessels is maintained even during severe hypothermia (20˚C).[40]

Recommendations and Suggestions

Figure 1 provides a flow diagram for determination of BD/DNC in persons treated with TTM.

1. It is recommended that practitioners be educated about the effects of hypothermia on both elimination of medications and determination of BD/DNC.
2. If, after rewarming a person who was treated with TTM, their exam appears consistent with BD/DNC, it is recommended that neuroimaging be obtained to assess for both severe cerebral edema and brainstem herniation consistent with severe intracranial hypertension.
3. If there is evidence of severe intracranial hypertension on neuroimaging 24 hours after rewarming to ≥ 36˚C, it is recommended that an assessment for recent administration of CNS depressing medications or other confounders should be performed.
4. If CNS depressing medications were recently administered to a person who 1) was treated with TTM, 2) has an examination that appears consistent with BD/DNC, and 3) has neuroimaging evidence of severe intracranial hypertension, it is recommended that:
    a. The clinical examination be delayed until at least 5 elimination half-lives of the drug administered with the longest half-life pass before performing an evaluation for BD/DNC, taking into consideration that drug metabolism can be delayed in the setting of hepatic/renal dysfunction, or
    b. Drug levels be obtained to ensure they are ≤ therapeutic levels before performing an evaluation for BD/DNC, or

c. An ancillary brain blood flow study be performed in addition to the clinical evaluation and apnea test to make a determination of BD/DNC.

5. It is recommended that if an imaging study shows evidence of severe cerebral edema and brainstem herniation consistent with intracranial hypertension and *no* CNS depressing medications were recently administered and there are no other confounders, an examination for determination for BD/DNC be made.

6. It is recommended that, if an imaging study does *not* show evidence of severe cerebral edema and brainstem herniation consistent with intracranial hypertension, a determination for BD/DNC should not be performed.

Questions to Inform Research Agendas

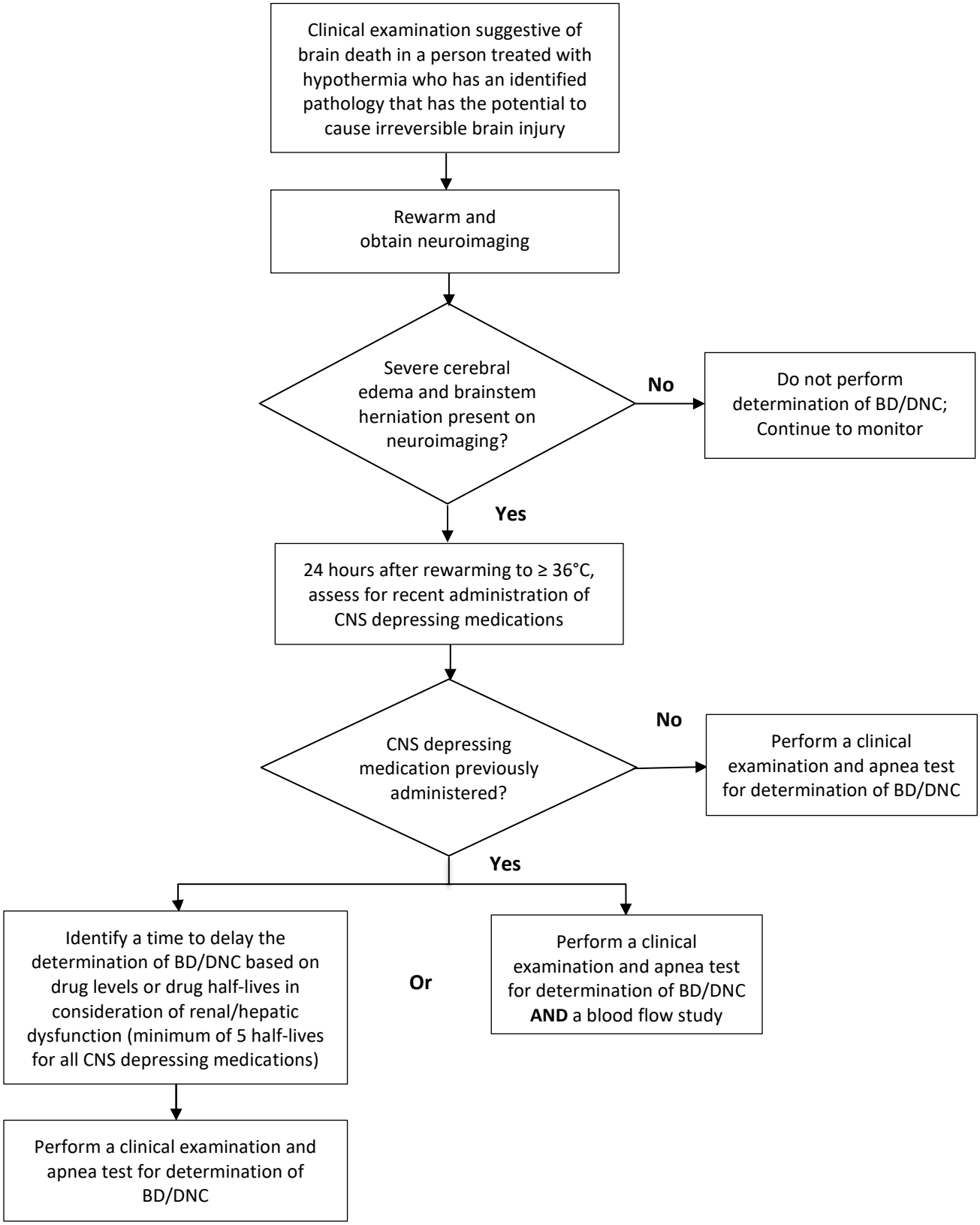
1. For each population treated with TTM, what are the determinants that predict progression to BD/DNC?

2. For patients treated with TTM who appear to fulfil clinical criteria for BD/DNC and do not have herniation on neuroimaging, what is the incidence and predictors of reversibility (resumption of brain function)?

3. In the presence of neuroimaging evidence of cerebral edema and herniation, what is the minimum time period after rewarming that a clinical determination is reliable?

4. When anoxic brain injury occurs under hypothermic conditions (e.g. cold-water drowning), should different observation times be considered?

Figure 1. Flow diagram for determination of BD/DNC in persons treated with TTM



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