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Pharmacologic Management During Therapeutic Hypothermia

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ABSTRACT
Out-of-hospital cardiac arrest continues to be associated with high morbidity and mortality as the mortality rate has been documented to be as high as 90% in patients who experience the insult at home. For those who survive, more than 50% will have some form of brain damage. Despite the devastation of this event, therapeutic options for improving outcomes in this population are unfortunately limited. However, therapeutic hypothermia has been evaluated in 2 landmark randomized, controlled trials in patients who experienced an out-of-hospital cardiac arrest with the results showing an improvement in both neurologic outcomes and mortality. Providers must be familiar with the rationale behind the therapy, the physiological effects of the cooling and rewarming processes, and the pharmacologic management that aides in improved outcomes and minimizes complications.
Key words: cardiac arrest, pharmacologic management, shivering, therapeutic hypothermia

EACH YEAR approximately 450,000 Americans suffer from cardiac arrest, and the mortality rate is estimated at 90% for those patients who experience cardiac arrest at home. For those who survive, more than 50% will have some degree of brain damage (Callans, 2004; Pusswald, Fertl, Faltl, & Auff, 2000). Although multiple etiologies may exist that lead to the arrest, the end result is the same, a decrease in cerebral blood flow causing cerebral ischemia. Cerebral ischemia occurs when there is inadequate blood flow to the brain for more than 5 min and can result in a multitude of negative outcomes and sequelae (Negovsky, 1988). The negative physiologic effects that occur after resuscitation can be counteracted by hypothermia. Physiologic benefits from hypothermia include a decrease in metabolic rate and free radical production (Keresztes & Brick, 2006; Smith & Bleck, 2002). The rationale behind therapeutic hypothermia improving neurologic outcomes stems from hypothermia reducing the rate of various chemical reactions involved with reperfusion injury

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Table 1. Mechanisms of action of therapeutic hypothermia

Rationale of Therapy in Patients After Cardiac Arrest
Decreases the brain's metabolic rate for oxygen
• Increased oxygen to ischemic areas of the brain
Decreases intracranial pressure
Suppresses reperfusion injury by curtailing various chemical reactions
• Free radical production
• Excitatory amino acid release
• Calcium shifts
May act as an anticonvulsant

including free radical production. These reactions can result in mitochondrial damage and cell death. By taking advantage of the fact that for every 1°C decrease in body temperature, the cerebral metabolic rate decreases by 6%–7%, therapeutic hypothermia slows down these postresuscitation reactions and helps decrease negative outcomes (Keresztes & Brick, 2006; Rosomoff & Holaday, 1954). Table 1 provides a detailed review of the proposed mechanisms of action of therapeutic hypothermia (Bernard & Buist, 2003; Nolan et al., 2003).

Therapeutic hypothermia has been evaluated in patients who have return of spontaneous circulation (ROSC) after cardiac arrest in two landmark randomized, controlled trials to help limit the impact of decreased blood flow to cerebral tissue (Bernard et al., 2002; Hypothermia After Cardiac Arrest [HACA] Study Group, 2002). The HACA Study Group reported a decrease in mortality and an increase in favorable neurologic outcomes 6 months after cardiac arrest. Bernard et al. conducted a similar study in Melbourne, Australia. This group also reported that therapeutic hypothermia improved outcomes in patients who suffered from an out-of-hospital cardiac arrest who remained comatose after ROSC. Survival to hospital discharge, which included discharge to home or a rehabilitation facility, with good neurologic function was the outcome of interest in this trial and the investigators found a significant difference between the two groups in favor of those randomized to therapeutic hypothermia (Bernard et al., 2002). Holzer et al. (2005) found improved survival and functional outcomes in one of six patients who remained comatose after cardiac arrest who received therapeutic hypothermia. The International Liaison Committee on Resuscitation made recommendations in 2002 advising the use of this therapy in select patient populations and proposed its possible benefit in other groups that had yet to be studied on the basis of the outcomes of the randomized controlled trials (Table 2; Nolan et al., 2003). Therapeutic hypothermia is also recommended, when indicated, in post–cardiac arrest care per the 2010 American Heart Association guidelines (Field et al., 2010).

The pharmacologic agents utilized during therapeutic hypothermia are used in clinical practice on a daily basis but being familiar with their use in this unique clinical scenario is important. In the sections that follow, the pharmacologic management of these patients is discussed in detail and focuses on pain and sedation, rigor or shivering management, electrolyte replacement, anticonvulsant use, and other potential complications.

PAIN AND SEDATION MANAGEMENT

As the cooling phase is initiated, patients may shiver in an attempt to restore a more homeostatic temperature. To prevent shivering, analgesics and sedatives should be used as first-line therapy (Neumar et al., 2008; Nolan, et al., 2003). Morphine and fentanyl are the two most common analgesics and can be administered as boluses or continuous infusions. Fentanyl is typically preferred over morphine, because it is associated with less hypotension due to a lack of histamine release, less vasodilation, and can be used in patients with codeine allergies due to it being a synthetic

Table 2. 2002 International Liaison Committee on Resuscitation recommendations

Patient Criteria	Recommendation
Return of spontaneous circulation AND Comatose after an out-of-hospital cardiac arrest AND Initial rhythm of ventricular fibrillation	Cooled to 32°C–34°C for 12–24 hr
In-hospital cardiac arrest OR Initial rhythms other than ventricular fibrillation	Therapeutic hypothermia may be beneficial

opiate (Rosow, Moss, Philbin, & Savarese, 1982). In addition, morphine has an active metabolite, morphine-6-glucuronide, which accumulates in patients with renal insufficiency. Renal function may already be compromised either from the lack of blood flow during cardiac arrest or from the hypothermia, leading to the potential for accumulation of this metabolite. When comparing the potencies of these agents, fentanyl is 100 times more potent than morphine and has a rapid onset of action and short duration of action. However, fentanyl is eliminated via hepatic enzymes, which are slowed during cooling causing a decreased clearance of these pharmacologic agents by as much as 30% (Arpino & Greer, 2008). More research is needed to determine the effect of medication accumulation in this patient population.

Midazolam and propofol are the two most common sedatives utilized in this patient population. Both of these agents can also be administered as boluses or continuous drips. Midazolam is a benzodiazepine and as such has amnestic, anxiolytic, and sedative properties. Because midazolam has a shorter onset of action and duration, it is usually the preferred benzodiazepine for use as a continuous infusion in therapeutic hypothermia patients. Another benefit of midazolam is that it is more water-soluble and therefore results in less phlebitis than diazepam and lorazepam that require lipoidal vehicles like propylene glycol. A common side effect associated with midazolam is hypotension so frequent assessment of hemodynamic parameters is advised (Reves, Fragen, Vinik, & Greenblatt, 1985). Propofol, another common sedative hypnotic, has a short onset of action and duration but can cause hypotension so patients should be monitored closely. Given that little information, if any, is known about these patients when therapeutic hypothermia is initiated, patients who do not respond well to one sedative should be switched to the other. An example would be patients who have a history of alcohol abuse. These patients, depending on how much alcohol they consume, may be less likely to respond to propofol and therefore midazolam would be preferred, as the benzodiazepines are utilized in the management of delirium tremens.

RIGOR OR SHIVERING MANAGEMENT

If management with analgesics and sedatives does not reduce shivering, neuromuscular blockers should be considered. The disadvantage to using these agents is that seizure activity will be masked, and seizure activity may occur in the postresuscitation state. Neuromuscular blockers that are often used include vecuronium, atracurium, and cisatracurium, which are nondepolarizing neuromuscular blockers that can be titrated to the degree of blockade necessary to prevent shivering. However, the use of these agents varies from one institution to another. Once patients are started on a continuous

infusion of a neuromuscular blocker, train-of-four monitoring should be done. Train-of-four is done to monitor the depth of neuromuscular blockade and assists in dose titration. The difference between vecuronium and atracurium/cisatracurium is the body's method of elimination. Vecuronium is eliminated by both the kidneys and the liver so the medication is likely to accumulate in patients with damage to either of these organs. Atracurium and cisatracurium are eliminated by Hoffman elimination, ester hydrolysis that occurs in the plasma, so hepatic and renal insufficiencies do not result in accumulation of these agents (Arpino & Greer, 2008; Bernard & Buist, 2003; Neumar et al., 2008). Even though atracurium and cisatracurium are eliminated differently, it is important for health care providers to be aware that the rate of Hoffman elimination is decreased by hypothermia (Arpino & Greer, 2008; Tortorici, Kochanek, & Poloyac, 2007). During therapeutic hypothermia with neuromuscular blockade, patients lose their corneal reflex and the ability to maintain eye closure. While paralyzed, topical therapies such as artificial tears and petrolatum aid in preventing corneal abrasions (Lenart & Garrity, 2000).

Shivering prevention can also include: α_2-adrenergic agonists such as clonidine and dexmedetomidine, meperidine, dantrolene, and buspirone, although these agents have not been studied in therapeutic hypothermia patients (Weant, Martin, Humphries, & Cook, 2010). Clonidine and dexmedetomidine decrease vasoconstriction because they are alpha-agonists and lower the shivering threshold. The mechanism responsible for lowering the shivering threshold is not well understood, but it is thought to be due to the alpha effects on the body's thermoregulatory centers. Dexmedetomidine has a higher affinity for alpha-receptors and is shorter acting than clonidine. However, both of these agents can result in hypotension and potentiate bradycardia so judicious monitoring of hemodynamic status is important. Meperidine is utilized in the postoperative setting to prevent shivering and could potentially be utilized in therapeutic hypothermia. This agent also has α_2-adrenergic properties in addition to effects on κ-opioid receptors. If meperidine is administered, providers should be cautious of prolonged sedation, respiratory depression and, most importantly, the accumulation of meperidine's toxic metabolites that can result in adverse events such as seizures. Drug accumulation may be enhanced in the setting of hypothermia and its clinical impact may be exacerbated by the already elevated risk of seizures in this population. Even less is known about dantrolene and buspirone in this patient population, but they too are options to consider when other agents have failed (Arpino & Greer, 2008). Significantly more research is needed in the area of shivering prevention and management to fully delineate the appropriate and most effective agents in this setting.

All of the agents described above should be individualized on a per patient basis. The Australian group utilized midazolam, doses ranging from 2 to 5 mg, and vecuronium 8–12 mg to prevent shivering (Bernard et al., 2002). In the HACA study, midazolam, fentanyl, and pancuronium were used. Midazolam and fentanyl were started on the basis of patient weight and then titrated as needed during the duration of therapeutic hypothermia and for ventilator management. Pancuronium was administered every 2 hr to prevent shivering (HACA, 2002).

ELECTROLYTE MANAGEMENT

Diuresis and hypovolemia are common in patients who are hypothermic. This results in electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypocalcemia and can contribute to the incidence of arrhythmias during the cooling phase. Rewarming often results in a shift of electrolytes with potassium being the most critical electrolyte impacted by this process. If patients are receiving potassium replacement during hypothermia, either potassium alone or as an additive in their maintenance fluids, these therapies should be stopped before rewarming to

prevent hyperkalemia. Because of the host of electrolyte disturbances that may occur, electrolytes should be measured frequently during both the cooling and rewarming phases. In addition, any abnormalities should be corrected back to within normal limits as quickly as possible. Magnesium is important because it acts as a vasodilator and can facilitate cooling by reducing the shivering threshold. The antiarrhythmic properties of this agent can also be beneficial due to the increased risk of arrhythmias during cooling. Blood glucose should be monitored closely in these patients as hypothermia results in elevations due to a delay in insulin secretion from the pancreas and insulin resistance (Neumar et al., 2008; Nielsen et al., 2011).

ANTICONVULSANT MANAGEMENT

Even though hypothermia may act as an anticonvulsant, it also has the potential to lead to a decrease in the seizure threshold. Thus, seizures may occur and can be difficult to control. In a recent prospective observational study, seizure incidence was reported at 24% (Nielsen et al., 2011). Seizures in this setting have also been described as being harder to manage with medications. Phenytoin and thiopental have been evaluated in animal studies in which they were found to have a neuroprotective effect; however, a trial evaluating thiopental in humans after cardiac arrest did not show a benefit. If seizure activity does occur in these patients, they should be promptly treated with benzodiazepines (e.g., midazolam), phenytoin, valproic acid, barbiturates, or propofol. Seizure prophylaxis in these patients has yet to be evaluated (Neumar et al., 2008). Electroencephalograms should be considered in these patients if they are paralyzed (Hovland, Nielsen, Kluver, & Salveson, 2006).

OTHER POTENTIAL COMPLICATIONS

In addition to the patient care issues described above, hemodynamic instability and infection are two other potential complications. Hypothermia results in an increase in systemic vascular resistance, thereby reducing cardiac output. For this reason, patients may have arrhythmias during the cooling phase with bradycardia occurring most frequently. Monitoring to ensure adequate perfusion is necessary as a decrease in heart rate is expected with hypothermia. Rewarming results in hypotension due to vasodilation so fluids, at room temperature or above, should be available to maintain the patient's mean arterial blood pressure through volume resuscitation (Bernard & Buist, 2003; Nielsen et al., 2011).

As demonstrated in the HACA study, hypothermia can also suppress the immune system, which has the potential to result in an increase in infection rates. Pneumonia was more common in the patients who were randomized to the hypothermia group, but the results were not statistically significant (37% compared with 29% in the normothermia group; HACA, 2002). In addition to the immune system, hypothermia also affects the hematologic system. During the cooling phase, the number of platelets and the functionality of existing platelets decrease. These and other changes result in prolonged clotting times and an increased risk of bleeding, so patients should be monitored closely for signs and symptoms of bleeding (Bernard & Buist, 2003; Neumar et al., 2008).

FUTURE RESEARCH ON PHARMACOLOGIC MANAGEMENT

Research evaluating the benefit of therapeutic hypothermia is still needed on patients suffering from initial arrhythmias other than ventricular fibrillation and pulseless ventricular tachycardia and patients who suffer from an in-hospital cardiac arrest as the data to date focus on out-of-hospital cardiac arrest. More pharmacokinetic data on the medications utilized in the management of therapeutic hypothermia and its complications would aid in the management of therapeutic hypothermia patients including the duration of action of medications used due to lower metabolic rate

during the cooling and rewarming phases. Data on medications other than analgesics, sedatives, and neuromuscular blockers would also be of great value to health care providers caring for these patients.

CONCLUSION

Therapeutic hypothermia appears to be an effective therapy for patients who have ROSC after cardiac arrest. Two landmark trials to date have shown a benefit in patients with out-of-hospital cardiac arrest, who have initial rhythms of ventricular fibrillation and pulseless ventricular tachycardia, but there is potential for this therapy to work in other rhythms. Patients who meet criteria similar to the HACA and Australian studies should be considered for this therapy. Cooling should be initiated as soon as possible and maintained at 32°C–34°C for 12–24 hr. Methods to induce cooling and then aid in rewarming the patient include external and internal devices and intravenous fluids. Pain and sedation management should be initiated to control the patient's shivering. Neuromuscular blocker therapy should be considered if analgesics and sedatives alone are not effective. Once the cooling phase is complete, rewarming should be started slowly. Monitoring is crucial during both cooling and rewarming as arrhythmias, electrolyte disturbances, and adverse effects may occur.

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