Case Report

Prolonged and profound therapeutic hypothermia for the treatment of “brain death” after a suicidal intoxication. Challenging conventional wisdoms

Abstract

Therapeutic hypothermia has been reported to improve the neurologic outcome of comatose survivors of out-of-hospital cardiac arrest. The use of therapeutic hypothermia in patients who have had an acute ischemic-hypoxic brain injury after a suicidal intoxication has not been previously reported.

We present the case of a young woman who presented comatose to our emergency department after attempting suicide by ingesting diazepam and a bottle of antifreeze (ethylene-glycol). Despite aggressive supportive care, the patient progressed to what appeared to be clinical brain death. At this point, the patient was managed with therapeutic hypothermia for 36 hours. The patient awoke within 48 hours of rewarming and made a complete and full neurologic recovery.

In conclusion, this case has important implications in the management of patients who have had an acute ischemic-hypoxic brain injury. Inappropriately labeling such patients as “brain dead” will result in the failure to institute therapeutic hypothermia and other advanced neuroprotective interventions in patients who could be salvaged with a good neurologic outcome.

Suicidal and accidental toxin exposure are a major health care problem with approximately 2.5 million cases and more than 1000 deaths being reported to Poison Control Centers in the United States each year [1]. Analgesics, sedatives/hypnotics, antidepressants, and alcohols account for most deaths with cerebral ischemia-hypoxia being the commonest pathophysiologic process leading to demise [1]. Many of these patients present to the emergency department (ED) with severe anoxic brain injury that usually progresses to brain death [2,3]. We present the case of a young woman who presented comatose to our ED after attempting suicide by ingesting diazepam and a bottle of antifreeze (ethylene-glycol). Despite aggressive supportive care, the patient progressed to what appeared to be clinical brain death. At this point, the patient was managed with therapeutic hypothermia (TH) for 36 hours. The patient awoke within 48 hours of rewarming and made a complete and full neurologic recovery.

A 24-year-old woman with a medical history of fibromyalgia and a previous suicide attempt (by cutting her wrists) was found unconscious by her family. Unbeknown to her family, she had sent a text message to a friend 13 hours previously stating that she had just overdosed on diazepam (about 10 pills) and antifreeze. The emergency medical personnel found the patient comatose with a Glasgow Coma Score (GCS) of 3, cyanotic, and agonal respirations. She was intubated in the field and transferred to our ED. On presentation, her blood pressure was 90/40 mm Hg, pulse rate was 140 beats per minute with a temperature of 38.8°C. Her GCS was 3 with no response to noxious stimuli, unequal nonreactive pupils (left, 4 mm; right, 2 mm), no corneal reflex, and minimal gag reflex with agonal respirations. Pertinent laboratory studies included a white blood cell count of 31.2 × 10⁹/L with 84% neutrophils, hemoglobin level of 17.6 g/dL, an international normalized ratio of 1.29, sodium of 150 mmol/L, potassium of 4.6 mmol/L, chloride of 118 mmol/L, total carbon dioxide of 5 mmol/L, blood urea nitrogen of 12 mg/dL, creatinine level of 1.6 mg/dL, glucose of 92 mg/dL, lactate of 17.1 mg/dL (4.5-19.8), β-hydroxybutyrate of 2.9 mg/dL (0.2-2.8), and creatinine phosphokinase of 633 IU/L (25-185). Arterial blood gas analysis (on mechanical ventilation) demonstrated a pH of 6.76, PCO₂ of 32 mm Hg, PaO₂ of 345 mm Hg, bicarbonate of 4 mmol/L, and an anion gap of 27 mmol/L. Liver function tests were within normal limits. Toxicology tests were positive for benzodiazepines but negative for all other toxins and drugs. Serum osmolarity was 482 mOsmol/kg with an osmolar gap of 173 mOsmol/kg. Portable chest radiograph demonstrated a right lower lobe pneumonia (aspiration pneumonia). Brain computed tomographic (CT) scan was reported to show “diffuse cerebral edema with effacement of sulci, ventricles, and basal cisterns” (see Fig. 1). The patient was seen by the neurology service whose impression was that of impending herniation (see Fig. 2). The family was informed of the grim prognosis, and “Gift of Life” (an organ procurement service) was contacted. The patient was transferred to our medical intensive care unit where treatment of ethylene-
glycol poisoning was initiated; this included intravenous fomepizole, dialysis, and a bicarbonate infusion [4]. Within 8 hours of initiating specific treatment of ethylene-glycol poisoning and approximately 30 hours after the drug overdose, the patient was noted to have fixed and dilated pupils with no gag reflex and absent spontaneous respirations. The patient’s acid-base status had normalized at this point, and the ethylene-glycol level was less than 20 mg/dL. Despite the patient appeared to have progressed to brain death and as an extraordinary salvage intervention and with the consent of the family, we started TH using our “postcardiac arrest” hypothermia protocol. This entailed the use of ice-cold intravenous saline, external cooling using a cooling jacket and blankets (Blanketrol III, Cincinnati Sub-Zero, Cincinnati, Ohio), and iced bags of saline placed on either side of the neck. Propofol (80 μg/kg per minute) was used for “sedation” and neuroprotection [5]; a neuromuscular blocking agent was not used. Norepinephrine was titrated to maintain a mean arterial pressure of greater than 70 mm Hg, and the ventilator was adjusted to optimize oxygenation and acid-base status. Although we had aimed to maintain the patients’ temperature between 32°C and 34°C, her core body temperature fell to 30°C. As she remained hemodynamically stable at this temperature, we elected to keep her temperature between 30°C and 32°C for up to 36 hours followed by a slow rewarm (see Fig. 3). The patient required ongoing dialysis for oliguric acute renal failure. The patient “awoke” with rewarming, and we were able to extubate her 48 hours later. Within a few hours of extubation, she was “texting” and talking on her mobile phone. Repeat head CT scan (see Fig. 4) and magnetic resonance imaging at this time showed resolving cerebral edema with a right occipital infarct. A detailed neurologic examination (including visual field examination) failed to detect any major neurologic deficit. Apart from amnesia, beginning the day of her suicide attempt, the patient’s memory and cognition appeared normal. The patient required short-term hemodialysis until recovery of renal function.

**Fig. 1** Head CT scan on presentation to hospital.

**Fig. 2** Neurology service note.

**Fig. 3** Time course of temperature and bicarbonate.

**Fig. 4** Head CT scan after extubation.
This case is noteworthy for a number of reasons. Firstly, we describe the use of prolonged deep hypothermia for severe cerebral edema after a drug overdose. The use of therapeutic hypothermia for this indication has not been previously reported. Furthermore, the most recent advanced cardiac life support guidelines and expert opinion in the field recommend a target temperature for therapeutic hypothermia of 32°C to 34°C for 12 to 24 hours [6-8]. We postulate that more prolonged hypothermia (ie, up to 36 hours) and lower temperatures (ie, 30°C-32°C, if tolerated) may have additional neuroprotective benefits above and beyond that associated with standard hypothermia protocols. However, most important, this case challenges the conventional practice and “wisdom” regarding the diagnosis and management of apparent “brain death” after a hypoxic-ischemic insult.

Brain death is defined as the complete and irreversible absence of all brain function [9]. The Uniform Determination of Death Act, drafted in 1980 and published the following year in the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, has 2 distinct definitions of death: “an individual who has sustained either (i) irreversible cessation of circulatory and respiratory function or (ii) irreversible cessation of all functions of the entire brain including the brainstem” [10]. Although the process for determining death was not stated, the Uniform Determination of Death Act states that “determination of death must be made in accordance with accepted medical standards.” In 1995, the American Academy of Neurology published guidelines for determining brain death in adults, setting prerequisites, and defining confounding factors in determining brain death and stating that the clinical examination is the primary mechanism for determining brain death [11]. Although the concept of brain death is accepted clinically, ethically, and legally in the United States, there is no national standard for the determination of brain death. There is evidence that variability and inconsistency in the process of determining brain death exist in both clinical settings and in State statutes [12]. Greer and colleagues [13] reported major differences in the brain death guidelines among the leading neurologic hospitals in the United States. Furthermore, there is little guidance on the diagnosis of brain death after an anoxic insult. It has been recommended that a period of observation longer than 6 hours is necessary to determine whether the hypoxic-ischemic injury is so severe that cytotoxic edema will develop throughout the brain leading to raised intracranial pressure and brain death and that evidence of diffuse cerebral edema be demonstrated on CT or magnetic resonance imaging [14]. However, in the study by Greer and colleagues [13], only 16% of hospitals mention a specific waiting period for cardiac arrest patients (anoxic injury), with a waiting period that varied from 6 to 24 hours. On the surface, our patient met all the criteria for brain death, namely an acute neurologic catastrophe compatible with the clinical diagnosis of brain death, coma (GCS of 3), absence of brainstem reflexes, a waiting period that exceeded 6 hours, severe cytotoxic edema on CT scanning, normothermia, and correction or her metabolic/acid-base status at the time that cooling was initiated [11]. This case has important implications as inappropriately labeling a patient as “brain dead” will result in the failure to institute therapeutic hypothermia, and other advanced neuroprotective interventions in a patient that could otherwise be salvaged with a good neurologic outcome.

Another interesting point of this case was the late application and prolonged duration of profound hypothermia. In the area of TH, 2 landmark studies published in 2002 demonstrated the beneficial effects of hypothermia on neurologic outcome in comatose survivors of out-of-hospital cardiac arrest [15,16]. The 2 studies form the basis for current practice, which includes initiating hypothermia within the first 6 hours of the anoxic insult (out-of-hospital cardiac arrest), targeting a temperature of 32°C to 34°C and providing TH for 12 to 24 hours. Therapeutic hypothermia has, however, been successfully used for other conditions including near-drowning, traumatic head injury, neonatal asphyxia, and cerebral edema because of liver failure [17-19]. Our case suggests that the conventional indications, target temperature, and time frame for the initiation of TH require reevaluation.

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