Ketamine Use Post Cardiac Arrest

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abstract

Return of Spontaneous Circulation (ROSC) is the immediate goal and successful outcome of CPR. However as the AHA ACLS algorithm series shows we are by no means done but need to recalibrate and deal with a new patient, a very sick one. Somewhere in a youtube lecture on this subject a professor characterizes the post CA patient as like someone in septic shock with a TBI and, oh yeah, a heart attack… Post cardiac arrest (CA) patients have a host of multi-systemic issues on top of the original cause of the CA. Neurological issues include a brain starved of oxygen and the subsequent ischemia/reperfusion injury when circulation returns. Electrical irregularities can result in seizures and inflammatory responses can worsen ICP. In fact neurological deficits are very common after CA but are not well understood. TV shows have a slightly skewed notion of successful CPR but badly misconstrue neurological outcome post arrest: “Characters on medical dramas were nine times more likely to survive with good neurologic outcomes than real patients.” (Augoustides, 2023) Outside of popular culture, the the effects of CA on the brain and nervous system needs more study. One such area of research is as patients often have need for sedation or analgesia the choice of which can affect hemodynamics as well as cardiac and pulmonary function. Sedation can also mask neurological function making assessment difficult. A number of studies have indicated the ketamine can have neuroprotective effects while supporting hemodynamic stability making it a useful sedative/ analgesic for this context.

Post Cardiac Arrest Care

To address the lack of clinical studies on the overall management of CA patients the American Heart Association Emergency Cardiovascular Care Committee and the Neurocritical Care Society cosponsored an expert panel (Hirsch, et al, 2024) on postarrest care topics. The authors note that many topics like TTM have a lot of research to refer to but others have little or none. The focus of this panel was to generate topic statements and come to general consensus as their relevance. “Topics were identified and prioritized by the panel and arranged by organ system to facilitate discussion, debate, and consensus building. Statements related to postarrest management were generated, and 80% agreement was required to approve a statement.” The topic breakdowns are: neurological, cardiac, pulmonary, hematological, infectious, gastrointestinal, endocrine, and general critical care management (Hirsch, et al, 2024).

The range of topics shows how varied the post arrest patient can be. The “Hs and Ts” very possibly still need to be addressed so CA does not reoccur. Recirculation brings with it ischaemia/ reperfusion toxicity. Hemodynamics are unstable, endogenous catecholamines depleted. A general inflammatory response constricts vessels and slows perfusion. Pulmonary aspiration and seizures are common post ROSC. And (though most folks are unresponsive after ROSC) if the person is somewhat conscious they

are dealing with significant pain and trauma. Multiple systems under attack all at the same time.

The ACLS post CA care algorithm checks whether or not the patient can follow commands. If not then the critical care includes targeted temperature management, MRIs of the brain and EEGs as neurological recovery is primary. In general the outcomes are not good one study of OHCA neurological outcomes after PEA (Stead, et al., 2022) showed that with 235 patients, 26% made it to "sustained ROSC" and 7% left the hospital. But only 3% overall had good neuro outcomes (measured by a Cerebral Performance Categories (CPC) score of 1).

Hirsch, et al, (2024) in their breakdown note the following neurological subtopics:

- brain oxygenation
  - perfusion
  - edema and ICP
- seizures
- sedation and analgesia

When discussing seizures the authors note a problem related to sedation - barbiturates are effective for treatment of seizures but "can confound neurological examination for several days, given their long half-lives and sedative effects" (Hirsch, et al, 2024). Ketamine is identified as a "third line treatment" for seizures and might have less of a confounding impact on a neuro assessment.

Sedation and analgesia is commonly used for mechanically ventilated patients as well as ones undergoing TTM. More generally sedation medications "provide comfort, prevent recall and reduce the metabolic demands of shivering and other motor activity" (Hirsch, et al, 2024). The potential negative effects include vasodilation and a drop in blood pressure; disruption of normal ventilation; changes in pH and muscular weakness - in addition to the confounding effect already mentioned. It is important to consider that sedation under TTM can be prolonged due to reduced metabolism of the drug due to hypothermia.

Hirsch, et al, (2024) note the following statements the percentage indicated shows the consensus in the group.

Sedation and Analgesia Statements

1. The goals of analgesia and sedation during temperature control after CA are to provide comfort, to reduce shivering, and to prevent recall during NMB (100%, 21/21).
2. Short-acting sedative and analgesic agents are preferred for patients in post-CA coma undergoing temperature control to reduce the duration of mechanical ventilation, time to awakening, and confounding of delayed prognostication (100%, 21/21).

3. Propofol, remifentanil, and fentanyl are favored over midazolam and morphine infusions (85.7%, 18/21).
4. Use NMB as needed during temperature control rather than as a continuous infusion. In addition, it is important to note that NMB may mask seizures in unmonitored patients (95.3%, 20/21).

Ketamine is not noted here except in a paragraph on “short-acting sedative and analgesic agents”. However the expert panel discussion gives a framework to understand what to consider when needing to use sedation in post CA care.

Sedation and Cardiac Arrest - PreHospital and ED

Common use cases for sedation in the ER and PreHospital include: rapid sequence intubation; agitation/delerium; procedural sedation; trauma. Engstrom, et al., (2023) note that in the case of RSI the choice of induction agent is critical when dealing with patients in shock or more specifically sepsis (etomidate performed slightly better than ketamine in this context). The recommendation is to exercise “caution when using ketamine in patients that may be catecholamine depleted on presentation and subject to hypotension and myocardial depression with ketamine use”. The authors note that there might be a discrepancy in the data: “One reason for the unexpected increase in hypotension found with ketamine in these two studies could be from its increased use in patients who were already hypotensive or at high risk of hypotension compared to the etomidate cohort.” (Engstrom, et al., 2023)

Engstrom, et al., (2023) indicate uncertainty for this hypotensive effect - “The mechanism of hypotension in septic patients receiving ketamine remains to be elucidated” - but there are a number of studies which point to this phenomenon.

Sharif et al., (2024) in their meta-analysis of procedural sedation and analgesia in ER and ICU considered over 8,000 patients looking at recovery time, adverse affects and patient success. The study considered a number of combinations of midazolam, opiates, ketamine, propofol, etomidate, and dexmedetomidine. In the conclusion “Compared with midazolam-opioids for procedural sedation and analgesia in the acute care setting, ketamine was associated with fewer respiratory adverse events, sedation recovery time is shortest with propofol, and patient satisfaction is highest using a combination of ketamine-propofol. Compared with ketamine-propofol, propofol-opioids may be associated with higher rates of respiratory and cardiac adverse events, and probably fewer gastrointestinal adverse events.” (Sharif et al., 2024)

McKinley, et al., (2021) in a large study at a tertiary-care, academic ED, where ketamine was used for “indications of agitation, procedural sedation, rapid sequence intubation, pain, sedation, seizure, status asthmaticus, and unknown” it was found to be versatile, safe and effective with less than 5% adverse effects reported.

Ketamine has a similar profile in prehospital studies - in one case over 11,000 patients in pre and in hospital care (roughly 50% for pain and trauma; 34% for agitation/AMS; 13% for cardiopulmonary issues and the rest for seizures). Adverse effects were tracked specifically hypoxic effect (8.4%) and hypercapnia (17.2%). There were 8 deaths where ketamine could not be ruled out as a cause (0.07%). (Fernandez,et al., 2021)

The 2020 position paper by The American College of Surgeons Committee on Trauma (ACS-COT), the American College of Emergency Physicians (ACEP), the National Association of State EMS Officials (NASEMSO), the National Association of EMS Physicians (NAEMSP) and the National Association of EMTs (NAEMT) similarly characterized ketamine as safe:

"This consensus document outlines the role of ketamine in the management of trauma patients in both the prehospital and hospital setting. Low-dose or sub-dissociative dose ketamine is a safe and effective analgesic that can be used for adult and pediatric trauma patients as an alternative to opioids, with opioids for synergistic effect, or for patients taking buprenorphine products with minimal effects on hemodynamic stability. Ketamine dissociative doses are safe and effective in adult and pediatric trauma patients and an excellent agent for induction of RSI, post-intubation sedation/analgesia and procedural sedation in the hypotensive trauma patient. Ketamine has a wide therapeutic window and thus can also be used for acute agitation and excited delirium." (Morgan, et al., 2021)

Ketamine and Neuroprotection

The research around CPR and post arrest recovery focuses on positive outcomes beyond survival. A number of recent studies look at the possibility that ketamine might have a "neuroprotective" effect in cases of TBI, ischemic stroke or the ischemia/reperfusion assault on the brain. There are not a lot of clinical trials in this area as Ornowska, et al. (2022) note in their "scoping review" of 181 studies. The authors note that "PCABI (post CA brain injury) is the primary cause of death in 68% of out-of-hospital CA patients, regardless of the etiology of the arrest."

The mechanism of injury is 2 fold. The "first hit" is the initial hypoxia from the CA which causes ischemia. The cerebrum requires around 20% of cardiac output and is quickly damaged during CA. An "excitotoxic cascade" begins quickly during cerebral ischemia, sodium/potassium pumps fail and the cells get flooded with calcium.

The "second hit" comes with reperfusion. "Increase in intra- cellular calcium levels during the primary ischemic event results in glutamate exocytosis onto the post-synaptic cell and subsequent upregulated expression of calcium-permeable NMDA receptors." (Ornowska, et al. 2022) The incoming oxygen cannot be properly used and ROS are formed. At the same time the general immune system response post CA causes cerebral edema and vasoconstriction. It is a stagnant mess and cell apoptosis cascades spread the damage.

Electrical conduction is affected, not only with seizures but also Cortical spreading depolarization (CSD). CSD is a spreading loss of “ion homeostasis, altered vascular response, change in synaptic architecture, and subsequent depression in electrical activity following an inciting neurological injury.” (Kramer, et al., 2016)

The consequences for post CA recovery are severe. “PCABI results in apoptosis of neurons, particularly in the highly metabolically active hippocampal and neocortical areas.” Results of this damage include “impairments in memory, executive functioning, and visual-motor skills” as well as “psychiatric comorbidities including depression, anxiety, and post-traumatic stress disorder.” (Ornowska, et al. 2022)

As an NMDA antagonist, ketamine can ameliorate the damage caused by excitotoxicity. Ketamine blocks the glutamate-containing vesicles ability to bind to the presynaptic membrane. “By preventing glutamate exocytosis and blocking calcium entry into the post-synaptic cell, intracellular calcium buildup may be diminished. If ketamine is administered following CA upon hospital admission for sedation, it may be effective in inhibiting the above-mentioned apoptotic cascades, thus resulting in improved neurologic outcomes.” (Ornowska, et al. 2022)

Research in the related areas of TBI and circulation arrest for cardiac surgery show a similar effect. Giuliano, et al., (2023) studied the effect of predosing canine subjects with ketamine before the procedure (hypothermic circulatory arrest (HCA)). “In ketamine-treated animals (n = 5), a total of 2.85 mg//kg of ketamine was administered IV half (1.425 mg/kg) of this dose was administered IV prior to initiation of cardiopulmonary bypass (CPB), and the other half was administered on re-initiation of CPB following HCA” The randomized control group was given normal saline.

The timing of the 2 doses was meant to cover the “2 hits” - both the initial ischemic injury and the reperfusion one. The researchers noted that “In our canine model of hypothermic circulatory arrest, treatment with ketamine led to significantly decreased neurobehavioral deficit scores (ie, less deficits) and reduced levels of CSF pNF-H, a marker of axonal and dendritic injury, and NSE, a marker of neuronal damage” additionally there were no “hemodynamic disturbances”.

With TBI the biggest historical concern with ketamine involved ICP. Ketamine was thought to increase ICP thus making it a dangerous option for traumatic brain injury. 3 studies indicated that ketamine did not increase and may decrease ICP ((Godoy, et al., 2021); (Gregers, et al., 2020); (Madsen, et al., 2021)). Sedation has many indications in brain injury. The patient if conscious is likely in much pain, and anxiety, perhaps agitated. They might have seizures. If unconscious, they are likely intubated. In both cases sedation should not increase cerebral metabolism nor ICP. TTM requires sedation as well.

The profile for ketamine as sedation under a TBI is similar to the characterization above for post CA. “Ketamine appears to inhibit cortical spreading depolarisations in both animal and human studies [1–3, 5], has been suggested to attenuate excitotoxicity, and has anti-inflammatory and anti-apoptotic effects. Ketamine administration could therefore be advantageous in critically ill patients with severe

acute brain injury." (Madsen, et al., 2021)

Ketamine is not a "magic bullet" as one author suggests (Augoustides, 2023). Sharif, et al. (2024) reminds that "there is no perfect pharmacological agent for procedural sedation and analgesia". Concerns about hypotension occuring when ketamine is given in a catecholamine depleted patient remain. Emergence phenomena can cause psychological trauma. Adverse affects with alcohol (and other substances) have been reported.

The possibility that it can have "neuroprotective" properties after CA or TBI (or possibly stroke and other cerebral insults) make it a very intruiging choice for sedation when the brain is facing severe threats from ischemia or reperfusion '2nd hit'. This is a key piece in the overall 'post cardiac arrest care' algorithm and clinical research in this area is needed.

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