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SEDATION AFTER CARDIAC ARREST AND DURING THERAPEUTIC HYPOTHERMIA

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Abstract

Mild therapeutic hypothermia (MTH) has improved neurological outcome of comatose patients after cardiac arrest (CA). Since the first clinical studies performed in this setting, sedation has always been associated with cooling procedures. The use of sedative drugs during MTH is required because it allows faster achievement and better maintenance of target temperature. Further studies are necessary to prove any potential neuroprotective effects of sedation after CA. No differences in clinical outcomes have been found among different drugs, except for those related to their intrinsic pharmacological properties: the association propofol/remifentanil provides a faster recovery of consciousness than midazolam/fentanyl but is associated with the need of more vasopressors to maintain stable hemodynamic. Moreover, pharmacokinetic properties of these drugs are often altered during MTH so that standard drug regimens could result in overdosing because of reduced clearance. Neuromonitoring could be helpful to titrate drugs' effects and detect earlier complications (i.e. seizure), while a wake-up test should be avoided during the first 24 hours after CA.

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Introduction

Sedation and analgesia were routinely used during critical illness. However, several studies clearly demonstrated that excessive sedation was associated with prolonged mechanical ventilation (MV) and longer intensive care unit (ICU) and hospital stays. Therefore, minimal use of sedative/analgesic agents has widely been implemented among ICU patients[1]. This strategy was also associated with a reduced development of neurologic complications, such as delirium[1]. Nevertheless, sedative agents play a pivotal role in the management of patients with an acute brain damage. In these patients, sedation has additional important functions[2]. Sedation, by reducing the cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood flow (CBF) and volume (CBV), increases the tolerance of the brain to secondary cerebral ischemia and it is part of the therapies used to decrease elevated intracranial pressure[3]. Overall, sedation acts to protect the brain against the extension of primary acute brain injury and secondary cerebral insults.

Cardiac arrest (CA) is a severe medical emergency, which requires immediate and specialized interventions. Despite many advances in resuscitative medicine, CA is still associated with a poor outcome, with a survival at discharge estimated between 8 and 15%[4-6]. Only few medical interventions have been associated with reduced mortality and disability rate[7]. Among them, the most important remain the quality of cardiopulmonary resuscitation (CPR), early defibrillation for shockable rhythms and mild therapeutic hypothermia (MTH, target 32-34°C) after recovery of spontaneous circulation (ROSC)[8-10]. Sedation has always been used in association with cooling methods, since the first non-randomized trials investigating MTH effects on outcome. Sedatives were often co-administered with muscle relaxants[11]. Thus, in contrast with recent data underlying the need of reducing or avoiding sedation in critically ill patients[12], CA survivors treated with MTH still remain a cohort of patients where the administration of sedative agents seems reasonable, at least in the early intensive care phase, without apparent adverse effects[13].

Aims of this review are then to define the role of sedation in the management of patients resuscitated from CA and their rationale during MTH, as well as the differences among different sedative drugs and how sedation can be monitored in this setting.

Why do we sedate comatose survivors after CA?

After CA, in comatose patients not eligible for MTH, a short cycle of sedation (first 24-48 hours) seems to be a wise strategy[14]. However, this has never been specifically investigated in trials and its use is transposed by other severe neurological conditions. Nevertheless, in a quite old randomized clinical study (RCT), a single (not continuous) dose of thiopental did not increase the number of patients showing cerebral recovery after CA when compared to standard of care, even if 20% of the thiopental vs. 15% of the standard-therapy group survived with "good" cerebral recovery[15]. Also, whether sedation should be titrated using sedation scales or an electrophysiogical end-point, such as electroencephalographic (EEG) burst-suppression, it remains unknown.

On the opposite, all patients eligible for MTH are routinely sedated[16]. The European Resuscitation Council guidelines state that "*patients need to be well-sedated during treatment with therapeutic hypothermia, and the duration of sedation and ventilation is therefore influenced by this treatment*"[17]. Similarly, American Heart Association guidelines underline that "*intermittent or continuous sedation and/or analgesia can be used to achieve specific goals*" in this setting[18]. Specifically, the goals to use sedation during MTH are the control of shivering and the reduction of agitation and ventilator dyssynchrony, which may be detrimental for

neurological recovery.

Particularly, shivering is activated when all the mechanisms that inhibit heat loss in response to reduced body temperature, such as peripheral vasoconstriction and piloerection, are overwhelmed and the initiation of involuntary contraction of skeletal muscles will generate heat and contribute to restore body temperature around 37°C[19,20]. Drugs directly inhibiting GABA receptors, as propofol or benzodiazepines, blunt the cerebral control on body temperature during MTH. This effect could be enhanced by the concomitant administration of analgesic agents, especially opioids. Drugs targets the hypothalamus, which is the main regulator of core temperature through afferent pathways and signals coming from sensitive neurons in the skin and blood and which is implicated in the initiation of shivering[21,22]. In patients with traumatic brain injury, Oddo et al.[23] showed that, during the use of external cooling to control persistent and refractory fever, the occurrence of shivering was associated with a significant reduction in partial pressure of oxygen in brain tissue ($P_{bt}O_2$). It is reasonable to assume that shivering could produce the same deleterious effects on brain oxygenation also in patients suffering from hypoxic-ischemic encephalopathy (HIE) after CA. Therefore different groups have developed protocols to titrate sedation in CA patients undergoing MTH, based on a stepwise approach, according to the clinical response, aimed to control shivering (Table 1)[22]. Thus, it should be mandatory to rapidly initiate sedation in comatose survivors after CA in whom MTH will be implemented and titrate sedative drugs to avoid shivering.

Another potential role of sedative agents after CA is the control of seizures. Both convulsive and non-convulsive seizures (NCSz) are common after CA[24]. In an observational study, Rittenberger et al.[25] found out that 12 out of 101 patients had NCSz after CA and half of them developed seizures in the first 24 hours since hospital admission. In a paediatric population, Abend et al.[26] showed that most of NCSz started during the late hypothermic or rewarming periods, when sedative agents are generally discontinued. All sedative drugs have anti-epileptic properties, which are further enhanced by the use of MTH. Thus, sedation in the early phase following hospital admission after successful resuscitation from CA could minimize the risk of increasing brain damage induced by uncontrolled epilepsy.

Sedation can also provide some neuroprotection after HIE. In the complex phenomenon generating secondary brain injury after CA, several mechanisms, such as brain-blood barrier disruption, activation of inflammation and consequent oxidative stress, mitochondrial dysfunction and excitotoxicity, are involved[27]. In an experimental model of murine middle cerebral artery occlusion, Adembri et al.[28] showed that propofol infusion, started immediately after occlusion, can reduce the infarct size by 30%. The hypothesized mechanism was an attenuation of calcium-induced cerebral mitochondrial swelling. Other experimental studies[29] elucidated the possible role of propofol in inhibiting NMDA receptor activation and the resulting reduced intracellular calcium influx, responsible for neuronal apoptosis. Harman et al.[30], in a laboratory model of fetal rat brain ischemic-reperfusion injury, demonstrated that all the anaesthetic drugs (i.e. propofol, thiopental, etomidate, and midazolam) had beneficial effects on membrane lipid peroxidation. However, ultrastructural findings and mitochondrial scoring confirmed that only propofol and midazolam provided the most effective neuroprotection.

Finally, as cerebral perfusion is often reduced with quite important oxygen needs in the early phase after reperfusion from CA[31], an increase in cerebral blood flow (CBF) could be helpful. Some human data on patients affected by subarachnoid hemorrhage without significant brain edema[32], suggested that isoflurane but not propofol was capable to increase CBF without significantly affecting intracranial pressure. New halogenates, such as sevoflurane and desflurane, may potentially provide additive neuroprotective effects after experimental global cerebral ischemia[33]. Furthermore, whether these effects could be clinically relevant in post-CA patients remains to be further studied.

Should we combine sedation with neuromuscular blocking agents?

The continuous administration of neuromuscular blocking agents (NMBA) in comatose survivors after CA has been studied by Salcioccioli et al.[34] In their retrospective analysis, patients who received continuous NMBA (only 18 out of 111) had a significant association with better survival (OR 7.23 [95%CI 1.56-33.38]) when compared to those not receiving NMBA. Unfortunately, these data do not support the use of NMBA is all patients with HIE undergoing MTH. Indeed, as the same authors point out, the few patients who received NMBA could simply be the more responsive and agitated after ROSC, so that clinician decided to start NMBA infusion only to optimize MTH achievement.

In clinical practice, NMBA should be administered as a bolus dose during the induction phase of hypothermia, as this would help to more rapidly achieve target temperature[35]. Thereafter, muscular relaxants must be used only as the last step to block muscular heat production, when sedative and analgesic agents have failed[26]. Indeed, as the shivering process rely on the activation of several cortical and subcortical areas[20], the simple inhibition of muscular response would not reduce the activity of central neurons, which would contribute to tissue hypoxia, metabolic disturbance and, potentially, to cell damage (Figure 1). Finally, muscle relaxants could be an option in those patients with severe myoclonus and poor neurological prognosis, when limitation of sustained therapy is decided.

Which sedative should we use?

If sedation has some rationale after CA, sedative agents have different properties. Their impact on cerebral metabolism and hemodynamics can be summarized as follows:

a) All the available drugs, except ketamine, reduce cerebral metabolism[36,37];

b) Volatile agents, despite a reduction in medium arterial pressure and cardiac output, can increase CBF because of local vasodilatation[38];

c) Ketamine increases cerebral perfusion, because of its intrinsic sympathetic activity. A recent systematic review concluded that ketamine is not associated with the increase in ICP[39] purported by older literature[40].

In 2010, Chamorro et al.[11] published a systematic review that aimed to define which sedative and analgesic protocol was the most frequently used for comatose survival after CA. The authors found 44 studies, developed in different countries and including patients from more than 65 ICUs. Midazolam and fentanyl were the most used sedative and analgesic drugs (in 39/44 and 33/44 studies, respectively), followed by propofol (13/44) and morphine (4/44). Pancuronium was the favourite NMBA, followed by cisatracurium (24/44 and 14/44 studies, respectively). It is important to note that not all the protocol included analgesia and NMBA. The conclusion of this review was that it existed a great variability in the protocols used for sedation and analgesia in CA survivors and that very often the drugs and the doses used did not appear to be the most appropriate. More recently, a RCT compared two different sedation protocols in 59 patients who underwent MTH: midazolam/fentanyl vs. propofol/remifentanil[41]. The primary outcome was the time from discontinuation of infusions to extubation or decision not to extubate (off-set time). Because of a low survival rate of this cohort, only 35/59 had sedation withdrawal and 17/35 were actually extubated. The offset time was significantly lower in patients receiving propofol/remifentanil than midazolam/fentanyl (13.2 [2.3–24] vs. 36.8 [28.5–45.1] hours, respectively, $p<0.001$). Nevertheless, patients receiving propofol/remifentanil needed norepinephrine infusions twice as often (23 vs. 12 patients, $p = 0.003$) than the others.

Taken together, these data point out a faster recovery of consciousness after propofol administration when compared to midazolam, which is counterbalanced by a more frequent risk of

hypotension with cerebral hypoperfusion. Thus, neither AHA nor ERC guidelines have suggested an optimal protocol for sedation after CA and during cooling procedures. In this setting, an interesting drug could be ketamine, which may exert neuroprotection by inhibiting the NMDA-receptor activation and mediating beneficial changes in apoptosis-regulating proteins or interfering with the inflammatory response to injury. Cardiovascular stimulation by ketamine may also improve cerebral perfusion, and this action may be advantageous in patients after brain injury[42]. Nevertheless, no clinical data are available on the role of ketamine on patients' hemodynamics and outcome and its possible effects on intracranial pressure in CA survivors are not well defined yet.

Some specific considerations should be reported for the use of dexmedetomidine, an α-2 receptor antagonist, in this setting[43-46]. Indeed, some experimental data have shown beneficial neuroprotective [47,48] and cardioprotective effects of this drug[49]. Also, dexmedetomidine has been implemented in several protocol of sedation in patients undergoing MTH as it could be useful, in addition to midazolam and propofol, to provide effective prophylaxis against shivering as well as an analgesic effect[22]. In clinical practice, these benefits could be counter-balanced by some predictable and negative cardiovascular effects, such as bradycardia and hypotension, which occur in up to 42% of patients; also, dexmedetomidine may cause profound left ventricular dysfunction and refractory shock[43-45]. Usually, these effects can be successfully treated with atropine, ephedrine, and volume supplementation, however cerebral hypoperfusion may occur and further enhance brain injury in CA patients. Thus, this drug could be used to control shivering during the cooling phase but its safety needs to be further studied in this setting.

One important caveat should therefore be considered when prolonged sedation is used in comatose CA patients. The use of MTH is associated with significant pharmacokinetic and pharmacodynamic alterations[50], which may result in sedative accumulation. A recent paper from Bjelland et al.[51] has shown that hypothermia slowed down drugs metabolism, consequently increasing blood concentration of morphine, propofol, midazolam and fentanyl. This effect was attributable to the decreased activity of the cytochrome P450, which was associated with a 7-22% reduction of drug metabolism per degree Celsius below 37°C during cooling[52]. Thus, if sedation is not titrated accordingly with reduced pharmacokinetic and pharmacodynamics, excessive sedation may prolong the time to obtain a reliable neurological examination in such patients and significantly influence the decision to limit life-sustaining therapies[53].

A practical approach could be as follow:

a) If the patient is hemodynamically stable and normotensive, propofol is the best initial choice for sedation, due to the rapid metabolism that allows for serial neurologic examinations soon after the agent is stopped;

b) In hypotensive patients, a low continuous midazolam infusion could be used;

c) Analgesia is commonly associated, using fentanyl or remifentanil infusions (Figure 1).

d) During MTH, titrate the sedative infusion, considering pharmacokinetic and pharmacodynamic alterations.

How can we monitor CA patients during sedation?

Monitoring of sedation has been poorly studied after CA. Continuous EEG during the first 48-72 hours is a good and reliable tool, but unfortunately it is not available in all ICUs yet[54]. An alternative is represented by bispectral index (BIS) monitoring, which is largely used during different type of surgery to determine the depth of anaesthesia and allows to adjust the amount of anaesthetic agent to the needs of the patient[55]. Nevertheless, the reliability of such techniques in monitoring anaesthesia after HIE is

questionable as the electrical activity of brain cortex could be altered after CA, which would significantly alter the interpretability of EEG findings. Moreover, the details of the algorithm used to create the BIS index are not available and one may argue that this device has never been validated to monitor anaesthesia in patients after an acute brain injury. Quantitative EEG (qEEG) is a technique that analyses EEG data transformed into a quantification of the amplitude or frequency by fast Fourier transformation. Some promising findings come from laboratory investigations where it has been used to successfully monitor brain recovery in rats after asphyxial cardiac arrest[56]. Some human data confirm the reliability of qEEG in neurocritical patients, to detect ischemia and NCSz[57]; however, whether this monitoring could give useful information to adjust sedation in CA survivors remains a unanswered question.

Thus, there is no available tool to accurately monitor the depth of sedation in CA survivors. EEG, BIS and qEEG should be more considered as tools with potential interest in predicting outcome after CA. Several studies have shown that some malignant EEG patterns, such as flat tracing and burst-suppression, or an unreactive EEG to external stimuli are strong predictor of poor neurological function after CA[24]. A recent pilot study also suggested that an elevated BIS index in the early phase after CA and cooling initiation was strongly correlated to neurological recovery[58].

When to stop sedation?

When the cooling period is almost finished, one of the most important challenges is when to discontinue sedative drugs. In critically ill patients, the concept of "wake-up test", i.e. daily withdrawal of sedation to evaluate patients' clinical status, has been developed in the last decade and has contribute to significantly reduce the duration of sedation, mechanical ventilation and ICU stay[59,60]. No study is available on the utility to perform this test in CA patients during the first 24 hours since ICU admission, i.e. the hypothermia phase. In patients with traumatic brain injury and subarachnoid haemorrhage, Helbok et al. showed that interruption of sedation resulted in increased shivering in 34% of patients and result in the development of brain hypoxia and could enhance the extension of brain injury[61]. Although these data cannot be directly extrapolated to CA patients, early interruption of sedation during MTH would increase the risk of shivering and potentially induce an abrupt raise in body temperature, which could be diminish the benefits of cooling on HIE[62]. Thus, sedative drugs should be discontinued only when core temperature is > 36°C.

Conclusions

Comatose survivals after CA have always been treated with sedation since MTH has been implemented in the management of HIE. Sedation appears to be necessary because it may reduce the incidence of seizures and facilitates the rapid achievement and maintenance of target temperature during cooling. There are no evidences to recommend one particular drug in the sedation protocol of such patients. Although sedation should be stopped only when normothermia is achieved, cooling reduces drug metabolism and may contribute to delay neurological recovery of comatose CA patients. Unfortunately, no device is available to adequately titrate sedation in this population. The questions whether sedative drugs can provide some neuroprotective effects in HIE and their role in CA patients not treated with MTH remains to be further studied.

Key points

- Sedation is recommended in comatose survivors after CA. Sedative and analgesic drugs yield effective control of agitation, ventilation dyssynchrony and shivering in the post-resuscitation

phase. Some evidences suggest also a possible additional neuroprotective effect in laboratory models of cerebral ischemia.

- Midazolam and propofol are the most widely used sedatives. Propofol would allow a faster neurological recovery but is also associated with a higher need for vasopressor therapy. NMBA are very useful at TH induction to achieve target temperature quickly. Continuous infusion of paralyzing agents is not mandatory during maintenance of TH but should be reserved to those patients who keep shivering despite optimized sedation/analgesia protocol.
- Considered the detrimental effects of abrupt increase in body temperature associated with shivering, we recommend to stop sedation infusion only when body temperature > 36°C. However, it should be reminded that MTH reduces drug metabolism and might prolong neurological recovery.
- No specific tool can be used to monitor the depth of sedation after CA. Continuous EEG, as BIS and qEEG devices, is indicted to give useful information on prognostication but not on the adequacy of sedation.

Conflicts of interest

The Authors have no conflict of interest to declare.

Figure Legend.

Figure 1: A practical algorithm to initiate sedation in comatose survivors after cardiac arrest. ROSC = return of spontaneous circulation; NMBA = neuromuscular blocking agent.

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Table 1. The Columbia anti-shivering protocol, adapted from Choi et al. [15]

Step		Intervention	Dose
0	Baseline	Acetaminophen	650-1000 mg q4-6h
		Buspirone	30 mg q8h
		Magnesium sulfate	0.5-1 mg/h IV - Goal: 3-4 mg/dl
		Skin counterwarming	Max 43°C
1	Mild sedation	Dexmedetomidine	0.2-1.5 mcg/kg/h
		or Fentanyl	25 mcg/h (starting dose)
		Meperidine	50-100 mg IM/IV
2	Moderate sedation	Dexmedetomidine and Opioids	Doses as above
3	Deep sedation	Propofol	50-75 mcg/kg/min
4	Neuromuscolar blockade	Vecuronium	0.1 mg/kg IV

Table 2. Sedation of Comatose Survivors after CA

Why sedate	To avoid shivering, agitation and ventilator dyssynchrony To prevent seizures To provide neuroprotection To facilitate the implementation of therapeutic hypothermia
Which sedative	Sedation should be initiated as soon as possible If the patient is hemodynamically stable and normotensive, propofol is the best initial choice for sedation, due to the rapid metabolism that allows for serial neurologic examinations soon after the agent is stopped. In hypotensive patients, a low continuous midazolam infusion or ketamine could be used. Combine analgesia, using fentanyl or remifentanil infusions. Combine NMBA at the induction of cooling
When to stop	Wake-up test could be detrimental during cooling Stop sedation when normothermia is achieved Drug accumulation may be expected because of reduce metabolism