Anesthesia and Analgesia Protocol During Therapeutic Hypothermia After Cardiac Arrest: A Systematic Review

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BACKGROUND: Present practice guidelines recommend sedative-analgesic and neuromuscular blocking administration during therapeutic hypothermia in comatose patients after cardiac arrest. However, none suggests the best administration protocol. In this study, we evaluated intensivists’ preferences regarding administration.

METHODS: A systematic literature review was conducted to identify clinical studies published between 1997 and July 2009. Selected articles had to meet the following criteria: use of hypothermia to improve neurologic outcome after cardiac arrest, and specific mention of the sedative protocol used. We checked drugs and dose used, the reason for their administration, and the specific type of neurologic and neuromuscular monitoring used.

RESULTS: We identified 44 studies reporting protocols used in 68 intensive care units (ICUs) from various countries. Midazolam, the sedative used most often, was used in 39 ICUs at doses between 5 mg/h and 0.3 mg/kg/h. Propofol was used in 13 ICUs at doses up to 6 mg/kg/h. Eighteen ICUs (26%) did not report using any analgesic. Fentanyl was the analgesic used the most, in 33 ICUs, at doses between 0.5 and 10 μg/kg/h, followed by morphine in 4 ICUs. Neuromuscular blocking drugs were routinely used to prevent shivering in 54 ICUs and to treat shivering in 8; in 1 ICU, their use was discouraged. Pancuronium was used the most, in 24 ICUs, followed by cisatracurium in 14. Four ICUs used neuromuscular blocking drug administration guided by train-of-four monitoring and 3 ICUs used continuous monitoring of cerebral activity.

CONCLUSIONS: There is great variability in the protocols used for anesthesia and analgesia during therapeutic hypothermia. Very often, the drug and the dose used do not seem the most appropriate. Only 3 ICUs routinely used electroencephalographic monitoring during paralysis. It is necessary to reach a consensus on how to treat this critical care population. (Anesth Analg 2010;110:1328–35)

The clinical use of mild hypothermia, defined as a reduction of body temperature to 32°C to 34°C, is the only treatment that has been proven effective in randomized clinical trials for improving neurologic outcome after cardiac arrest. In 2002, results of 2 clinical trials were published regarding the use of therapeutic hypothermia on unconscious patients resuscitated from out-of-hospital cardiac arrest; both demonstrated improved neurologic outcome,1,2 and one of them improved survival.2 These findings have been confirmed in other non-randomized studies and in recent systematic reviews and a meta-analysis.3–12 According to international guidelines, the use of therapeutic hypothermia is recommended for the treatment of comatose cardiac arrest patients. In 2003, the International Liaison Committee on Resuscitation advised that unconscious post–out-of-hospital cardiac arrest patients should be cooled when the initial rhythm is ventricular fibrillation.13 The statement also suggested that cooling may be beneficial after nonventricular fibrillation cardiac arrests.

Postcardiac arrest includes several pathophysiologic processes: brain injury; myocardial, hepatic, and renal dysfunction; as well as systemic ischemia/reperfusion response. The severity of these disorders is not uniform and will vary in individual patients based on the duration of the ischemic insult, the cause of cardiac arrest, and the patient’s prearrest state of health.14

Mild hypothermia should be implemented, whenever feasible, in addition to standard supportive and critical care. This supportive care should be adapted to both the specific patient situation and specific peculiarities of the hypothermic situation.

Lately, recommendations have been published for the general management of patients treated with hypothermia after cardiac arrest, but none suggest the best sedation-analgesia protocol.14–18 It must be emphasized...
that hypothermia induces significant pharmacokinetic and pharmacodynamic alterations of most drugs used, including sedatives, analgesics, and neuromuscular blocking drugs (NMBDs). A sedation-analgesic neuromuscular blockade strategy may influence the time of recovery of consciousness, and therefore initial prognostication after hypothermia discontinuation, mechanical ventilation time and complications, seizure detection and its early treatment, and other important factors such as the influence on hemodynamic status. The aim of this study was to evaluate and discuss the different protocols used in published studies, with the goal of suggesting 1 specific strategy for sedation-analgesia administration and monitoring.

METHODS

An electronic literature review was conducted based on EMBASE and MEDLINE/PubMed searches to identify all clinical studies published between 1997 and July 2009, using the following National Library of Medicine MeSH search terms: (hypothermia OR cooling OR temperature) AND (cardiac arrest OR postresuscitation). Animal studies and clinical case reports were excluded from analysis, and no language restrictions were applied. Selected articles had to meet the following criteria to be included: use of hypothermia to improve neurologic outcome in adult coma patients after cardiac arrest and specific mention of the sedative-analgesic and neuromuscular blockade protocols used during this treatment procedure. Studies published in different journals with different aims but performed in the same intensive care unit (ICU) and with the same study protocol were considered as a single study. Bibliographies of each selected study were hand searched to identify additional studies for consideration. We checked the type of drug and dose used, the reason for its administration, the specific type of neurologic and neuromuscular monitoring used, and the incidence of seizures detected during the procedure.

RESULTS

We identified 44 studies including 1892 patients and representing sedative-analgesic and neuromuscular protocols used in 68 ICUs from various countries. Forty-eight ICUs were located in 15 European countries: Austria,2,22,44,52 Belgium,2,25 Czech Republic,51 Denmark,48 Finland,2,32,47 France,27,34,46,50,61 Germany,2,49,55,60 Holland,43,59 Italy,2 Luxembourg,54 Norway,29,55,58 Slovenia,57 Sweden,43,62 Switzerland,30,31 and the United Kingdom46,39; 9 in the United States,24,28,39,40,53,58, 1 in Canada41,5 and in Australia,1,24; 4 in Japan25,26,42,57; and 1 in Israel.33

In 8 ICUs, there was no information about the specific type of sedative used, and in 6, it was possible to use either midazolam or propofol. In the remainder of the ICUs, midazolam was the selected sedative; in 39 ICUs, doses were between 5 mg/h and 0.3 mg/kg/h, and in 16, the midazolam dose was not specified. Propofol was used in 13 ICUs at doses up to 6 mg/kg/h; lorazepam was used in 1 ICU; and ketamine was used in 1 ICU (Table 1). Eighteen ICUs (26%) did not report using any analgesic during hypothermia, and in 9, the type of analgesic was not specified. Fentanyl was used in 33 ICUs at doses between 0.5 and 10 μg/kg/h; morphine was used in 4 ICUs, sufentanil in 2, and both buprenorphine and piritramide in 1 (Table 1).

NMBDs were routinely used to prevent shivering in 54 ICUs, to prevent shivering only during cooling in 1, and to treat shivering in 8 ICUs; in 4 ICUs, the reason for use was not specified, and in 1 ICU, its use was discouraged. Pancuronium was used in 24 ICUs, cisatracurium in 14, rocuronium in 10, vecuronium in 9, and atracurium in 4. In 6 ICUs, the NMBD used was not specified (Table 2). Four ICUs used NMBD administration guided by train-of-four (TOF) monitoring.30,31,41,47,56 Only 3 ICUs performed continuous monitoring of cerebral activity during the hypothermia procedure: 2 used the electroencephalogram (EEG)45,56 and 1 used the bispectral index (BIS).54 The occurrence of status epilepticus during the procedure was reported by 25 ICUs, with the percentage of incidence varying between 0% and 44%.

DISCUSSION

This systematic literature review shows important variability in the sedation-analgesia and neuromuscular blockade protocols used during therapeutic hypothermia in comatose survivors of cardiac arrest. Current practice guidelines recommend analgesic, sedative, and NMBD administration during therapeutic hypothermia procedures in these patients.11,14–16 However, none of the guidelines suggests the best sedation-analgesia administration protocol. This void could explain the major variability in the protocols. Survivors of cardiac arrest who are treated with therapeutic hypothermia are very susceptible to complications with the use of these drugs. First, they often have renal or hepatic dysfunction secondary to prolonged cardiac arrest, so metabolism and elimination of these drugs are delayed for an unpredictable amount of time. In addition, the myocardial dysfunction after cardiac arrest makes patients more susceptible to hemodynamic complications. Finally, induced hypothermia itself produces delays in metabolism and clearance of most drugs, modifying drug response, particularly potency and efficacy.19,20,63 Therefore, inadequate use of sedation and NMBDs prolongs recovery and also delays the time to reliable evaluation of neurologic status and prognosis. The longer ICU stays generally required for the implementation of therapeutic hypothermia for 12 to 24 hours may be associated with the allocation of more intensive care resources and with unknown additional costs. Although ICU stays may be longer, it is unclear whether the total hospital stay is longer. In addition, the extra costs of care may be justified because outcome is improved.

Midazolam was the sedative chosen by 57% of the ICUs studied. Nevertheless, its pharmacokinetic profile does not seem to be the most suitable in this situation. Midazolam metabolism may be altered in patients with hepatic dysfunction, and in renal dysfunction, their active metabolites could accumulate. In addition, Fukuoka et al.44 reported a 5-fold increase in midazolam plasma concentrations in traumatic brain-injured patients treated with hypothermia (32°C–34°C) compared with normothermic patients. This may be explained by the depressed CYP3A4 and CYP3A5 activity during hypothermia.19 Thus, once the administration of midazolam is interrupted, its sedative effect may be
unpredictably prolonged in patients undergoing hypothermia. In this study, great variability in chosen dosage was also observed. In some ICUs, midazolam is administered at 5 mg/h, but others administer it up to 0.3 mg/kg/h, an unjustifiably high dose.5 5 ICUs protocolize midazolam use at a dose >0.2 mg/kg/h. Obviously, a prolonged residual effect is more probable with the use of these higher doses.

The pharmacokinetic profile of propofol seems more adequate than that of midazolam, because neither this drug nor its metabolites accumulate to cause hepatic or renal dysfunction.66 However, its potential toxicity may be increased in hypothermia. In this situation, the plasmat concentration could increase up to 30% compared with the concentration achieved in normothermic patients receiving the same dose; reduced intercompartmental clearance between the central and peripheral compartments can probably justify this finding.63 Use of high-dose infusions has been associated with the propofol infusion syndrome, which includes significant cardiovascular toxicity.67
Table 2. Selected Neuromuscular Blockers, Type and Dose, in the Different Published Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Year of the study</th>
<th>Patients included</th>
<th>Neuromuscular blocker</th>
<th>Dose</th>
<th>Indication</th>
<th>Status epilepticus incidence and monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard et al.</td>
<td>Melbourne</td>
<td>1993–1996</td>
<td>22</td>
<td>Vecuronium</td>
<td>Not specified</td>
<td>To promote cooling, (withheld when cooled)</td>
<td>36%</td>
</tr>
<tr>
<td>Zeiner et al.</td>
<td>Vienna</td>
<td>1995–1996</td>
<td>27</td>
<td>Pancuronium</td>
<td>0.01–0.02 mg/kg/h</td>
<td>To prevent shivering</td>
<td>0</td>
</tr>
<tr>
<td>Nagao et al.</td>
<td>Tokyo</td>
<td>1996–1998</td>
<td>50</td>
<td>Pancuronium</td>
<td>Not specified</td>
<td>Small doses, as required</td>
<td>No data</td>
</tr>
<tr>
<td>Bernhard et al.</td>
<td>4 Australian ICUs</td>
<td>1996–1999</td>
<td>43</td>
<td>Vecuronium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>HACA</td>
<td>9 ICUs (Austria 2, Belgium 2, Germany 2, Italy 2, Finland 1)</td>
<td>1996–2001</td>
<td>137</td>
<td>Pancuronium</td>
<td>0.1 mg/kg</td>
<td>Every 2 hours to prevent shivering</td>
<td>7%</td>
</tr>
<tr>
<td>Feilberg et al.</td>
<td>Houston</td>
<td>1998–1999</td>
<td>9</td>
<td>Vecuronium</td>
<td>Infusion, Not specified</td>
<td>To control shivering</td>
<td>44% during rewarming</td>
</tr>
<tr>
<td>Hachimi-Idrissi et al.</td>
<td>Brussels</td>
<td>1999</td>
<td>16</td>
<td>Pancuronium</td>
<td>0.05 mg/kg/h</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Laurent et al.</td>
<td>2 French ICUs</td>
<td>2000–2002</td>
<td>22</td>
<td>Pancuronium</td>
<td>Not specified</td>
<td>1–4 mg/h</td>
<td>No data</td>
</tr>
<tr>
<td>Busch et al.</td>
<td>3 USA ICUs</td>
<td>2001–2002</td>
<td>13</td>
<td>Cisatracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Oddo et al.</td>
<td>Lausanne</td>
<td>2002–2004</td>
<td>137</td>
<td>Pancuronium</td>
<td>Bolus 0.1 mg/kg/TOF</td>
<td>To prevent shivering</td>
<td>34.8%</td>
</tr>
<tr>
<td>Scott et al.</td>
<td>Oklahoma</td>
<td>2003–2005</td>
<td>51</td>
<td>Atracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>20%</td>
</tr>
<tr>
<td>Al Thalenyan et al.</td>
<td>London (Canada)</td>
<td>2003–2007</td>
<td>37</td>
<td>Pancuronium</td>
<td>To prevent shivering</td>
<td>When indicated</td>
<td>18%</td>
</tr>
<tr>
<td>Kagawa et al.</td>
<td>Hiroshima</td>
<td>2003–2008</td>
<td>80</td>
<td>Pancuronium</td>
<td>TOF monitoring</td>
<td>To prevent shivering</td>
<td>21%</td>
</tr>
<tr>
<td>Bekkers et al.</td>
<td>Maastricht</td>
<td>2004–2005</td>
<td>43</td>
<td>Atracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Haugk et al.</td>
<td>Viena</td>
<td>2004–2005</td>
<td>28</td>
<td>Rocuronium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Rundgren et al.</td>
<td>Lund</td>
<td>2004–2005</td>
<td>34</td>
<td>Rocuronium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Bruel et al.</td>
<td>Caen</td>
<td>2004–2006</td>
<td>33</td>
<td>Atracurium</td>
<td>0.5 mg/kg/h</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Tiainen et al.</td>
<td>Helsinki</td>
<td>2004–2006</td>
<td>36</td>
<td>Pancuronium</td>
<td>0.05 mg/kg/TOF</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Bro-Jeppesen et al.</td>
<td>Copenhagen</td>
<td>2004–2006</td>
<td>79</td>
<td>Cisatracurium</td>
<td>0.06–0.12 mg/kg/h</td>
<td>To control shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Wolff et al.</td>
<td>Schwerin</td>
<td>2004–2006</td>
<td>49</td>
<td>Atracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Hammer et al.</td>
<td>2 French ICUs</td>
<td>2004–2006</td>
<td>22</td>
<td>Pancuronium</td>
<td>0.05 mg/kg/h</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Gal et al.</td>
<td>Brno</td>
<td>2004–2006</td>
<td>43</td>
<td>Rocuronium</td>
<td>0.5 mg/kg/h</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Kliegel et al.</td>
<td>Pittsburgh</td>
<td>2005–2006</td>
<td>20</td>
<td>Discouraged use</td>
<td>To prevent shivering</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Rittenberger et al.</td>
<td>Los Angeles</td>
<td>2005–2007</td>
<td>69</td>
<td>Atracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Stamm et al.</td>
<td>Luxembourg</td>
<td>2005–2007</td>
<td>45</td>
<td>Cisatracurium</td>
<td>0.1 mg/kg/h</td>
<td>To prevent shivering</td>
<td>8.9% of BIS®</td>
</tr>
<tr>
<td>Derwall et al.</td>
<td>5 hospitals, Aachen (Germany)</td>
<td>2005–2007</td>
<td>37</td>
<td>Rocuronium or pancuronium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Legriel et al.</td>
<td>Versailles</td>
<td>2005–2008</td>
<td>51</td>
<td>Cisatracurium</td>
<td>0.18 mg/kg/TOF</td>
<td>To prevent shivering</td>
<td>10% of EEG</td>
</tr>
<tr>
<td>Takeuchi et al.</td>
<td>Kitasato</td>
<td>2005–2008</td>
<td>25</td>
<td>Vecuronium</td>
<td>Not specified</td>
<td>To control shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Aghenta et al.</td>
<td>New York</td>
<td>2006</td>
<td>8</td>
<td>Cisatracurium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Jimmink et al.</td>
<td>Amsterdam</td>
<td>2006–2007</td>
<td>27</td>
<td>Rocuronium</td>
<td>Not specified</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Storm et al.</td>
<td>Berlin</td>
<td>2006–2007</td>
<td>52</td>
<td>Pancuronium</td>
<td>Repetitive doses Bullus</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
<tr>
<td>Pichon et al.</td>
<td>Limoges</td>
<td>Published in 2007</td>
<td>40</td>
<td>Pancuronium</td>
<td>To control shivering</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Nordmark et al.</td>
<td>Uppsala</td>
<td>Published in 2009</td>
<td>4</td>
<td>Rocuronium</td>
<td>Bolus or 0.15 mg/kg/h</td>
<td>To prevent shivering</td>
<td>No data</td>
</tr>
</tbody>
</table>

EEG = electroencephalographic monitoring; BIS = bispectral index; TOF = train-of-four.
unpredicted increase of plasmatic concentrations of propofol during hypothermia procedures could make patients more susceptible to this syndrome. In addition, its early identification is difficult because lactic acidosis, cardiovascular instability, and slow cardiac rhythms are common after cardiac arrest or during hypothermia procedures.

Ketamine and lorazepam use is limited and was recorded in only 1 ICU in this study. The pharmacokinetic profiles of these drugs do not seem to make them the most appropriate options either.

Another surprising finding of this review is that 26% of the ICUs did not report any analgesic administration in their sedation strategy. This approach does not follow the present guidelines, which suggest first administration of analgesics and second, if necessary, administration of sedatives.

Nearly 50% of the remainder of the ICUs used fentanyl as their preferred analgesic, but once again with a wide and unjustified variation in the dose chosen, between 0.5 and 10 \( \mu \)g/kg/h. Metabolism and clearance of fentanyl are modified during hypothermia; there are studies showing a decrease up to 3.7 times in the fentanyl clearance in this situation, so the high dose could produce significant delays in the awakening time after fentanyl infusion interruption.

Only 4 ICUs selected morphine as their analgesic, probably because its effect is unpredictable during hypothermia treatment; the effect of morphine could be increased because of active metabolite accumulation if renal dysfunction is present or it could be reduced because of a decrease in morphine receptor affinity in a hypothermic situation.

Most recommendations include using NMBDs to quickly achieve the hypothermia target and to avoid shivering during hypothermia treatment. Shivering produces undesirable responses, such as increased oxygen consumption, excessively laborious breathing, faster heart rate, and a general stress-like response. Shivering may be controlled with numerous drugs, including the most frequently used sedatives, but in these cases, it is necessary to use them at a high dose, with the possibility of inducing more hemodynamic instability. NMBDs are very effective in preventing and controlling shivering and are devoid of major adverse hemodynamic effects, giving them great advantages in hemodynamically unstable patients. However, their metabolism could also be affected in hypothermic situations and in patients with organic dysfunctions, especially during steroid NMBD use. Active metabolites of vecuronium and pancuronium accumulate in patients with renal dysfunction, producing undesired prolonged residual paralysis. Rocuronium metabolism is decreased if there is hepatic dysfunction. Thirty-three of the ICUs included in this study used pancuronium or vecuronium, and 10 selected rocuronium.

Monitoring of paralysis depth with TOF is recommended to prevent steroid NMBD accumulation, but this monitoring loses its utility during hypothermia. Peripheral nerve conduction is slowed by cooling and is not a reliable monitoring method at temperatures in this treatment range. Perhaps this point can justify the minimal use of this type of monitoring found in this review. Administration of paralytic drugs may mask seizure activity. Sometimes hypothermic patients are not treated with paralytic drugs, but in these cases, it is very difficult to distinguish between shivering and myoclonic activity. Status epilepticus may occur in a substantial proportion of patients after postanoxic injury, and unless patients are routinely monitored for seizure activity during continuous EEG monitoring, paralysis can cause diagnostic problems. Accurate identification is important because seizures are associated with worse outcome, may contribute to the burden of brain injury, and can be treated with antiseizure medications. For this reason, many authors recommend using continuous EEG monitoring during sustained neuromuscular blockade. In this study, 79% of the ICUs reported routinely using NMBDs to prevent shivering during a hypothermia procedure, but only 3 of them reported using continuous monitoring of brain electrical activity, either by conventional EEG or by BIS monitoring. Therefore, most ICUs cannot detect and do not treat status epilepticus after cardiac arrest. However, controlling epileptic seizures has not yet been demonstrated to improve neurologic prognosis. It is also important to emphasize that paralysis may mask insufficient sedation, and in animal experiments, it has been shown that the protective effects of hypothermia can be partially or even completely lost when animals are not sedated during hypothermia treatment.

Present recommended protocols for the management of patients treated with hypothermia share many basic aspects of treatment, such as early coronary angiography, early stabilization and normalization of cardiovascular variables, hemodynamic monitoring, and glycemia control, but none of the protocols addresses sedation, analgesia, and paralysis strategies. As has been shown, the variability in approaches is enormous, and choosing the wrong treatment could produce an increase in morbidity and perhaps in mortality. Each day, additional ICUs are starting to use therapeutic hypothermia as a treatment in comatose survivors of cardiac arrest, so it is time to define the best sedation strategy. Clinicians must carefully select drugs with the lowest possible toxicity in this specific situation to avoid delays in consciousness recovery time and therefore mistakes in the initial prognosis after hypothermia discontinuation, prolongation in mechanical ventilation time, complications derived from the latter, as well as the contribution to hemodynamic instability. It is necessary to detect seizures in paralyzed patients and to obtain data that could help with patient prognosis without interference produced by the chosen drug.

Since 2004, the ICUs of the Puerta de Hierro–Majadahonda University Hospital and the Guadalajara University Hospital have been using a protocol for the administration of sedation in combination with therapeutic hypothermia (Fig. 1). We use remifentanil with or without propofol as the sedoanalgesia regimen and cisatracurium, 0.1 mg/kg/h, as an NMBD to prevent shivering. Sedoanalgesia titration is guided by using the BIS Monitor (Aspect Medical Systems, Natick, MA). If the initial admission BIS value is <40, we initiate remifentanil at a dose of 6 \( \mu \)g/kg/h. If the BIS value is >40, we add propofol to maintain BIS values between 40...
and 60. Because the requirements of propofol in mild hypothermia are decreased to achieve the same effect, the BIS monitor enables us to administer the exact dose of propofol to reach the targeted BIS value and to avoid deleterious effects. We do not use TOF monitoring with a peripheral nerve stimulator to measure the depth of paralysis during therapeutic hypothermia, but we use it after rewarming. When rewarming is started, at a temperature of 36°C, cisatracurium perfusion is discontinued. When a TOF ratio is >0.9, propofol infusion is discontinued and we initiate a gradual reduction in the remifentanil dosage until recovery of consciousness. We think that with this protocol, we reach the goals of sedoanalgesia and neuromuscular blockade in patients admitted to therapeutic hypothermia after cardiac arrest because (1) it ensures adequate analgesia and sedation; (2) the abnormal epileptiform EEG waves can be identified on the BIS monitor and the different numerical data can help to detect nonconvulsive seizures; (3) we avoid accumulation of drugs that could distort later neurological examination; and (4) the protocol permits fast recovery of consciousness and neurologic examination after the sedation infusion is halted. However, it is important to emphasize that this protocol has not been tested against other protocols to show the theoretical advantages and BIS monitoring has not been validated in a hypothermia situation or in critically ill mechanically ventilated patients. For these reasons, the protocol can only be considered as a proposal for comparison with other protocols.

**AUTHOR CONTRIBUTIONS**

CC, JMB, and MAR helped to design and conduct the study, collect and analyze the data, and write the manuscript. JAS and BB helped to collect and analyze the data.

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