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Continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients☆

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ABSTRACT

Aim: Neuromuscular blockade may improve outcomes in patients with acute respiratory distress syndrome. In post-cardiac arrest patients receiving therapeutic hypothermia, neuromuscular blockade is often used to prevent shivering. Our objective was to determine whether neuromuscular blockade is associated with improved outcomes after out-of-hospital cardiac arrest.
Methods: A *post hoc* analysis of a prospective observational study of comatose adult (>18 years) out-of-hospital cardiac arrest at 4 tertiary cardiac arrest centers. The primary exposure of interest was neuromuscular blockade for 24 h following return of spontaneous circulation and primary outcomes were in-hospital survival and functional status at hospital discharge. Secondary outcomes were evolution of oxygenation (PaO_2:FiO_2), and change in lactate. We tested the primary outcomes of in-hospital survival and neurologically intact survival with multivariable logistic regression. Secondary outcomes were tested with multivariable linear mixed-models.
Results: A total of 111 patients were analyzed. In patients with 24 h of sustained neuromuscular blockade, the crude survival rate was 14/18 (78%) compared to 38/93 (41%) in patients without sustained neuromuscular blockade ($p = 0.004$). After multivariable adjustment, neuromuscular blockade was associated with survival (adjusted OR: 7.23, 95% CI: 1.56–33.38). There was a trend toward improved functional outcome with neuromuscular blockade (50% versus 28%; $p = 0.07$). Sustained neuromuscular blockade was associated with improved lactate clearance (adjusted $p = 0.01$).
Conclusions: We found that early neuromuscular blockade for a 24-h period is associated with an increased probability of survival. Secondarily, we found that early, sustained neuromuscular blockade is associated with improved lactate clearance.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) occurs in 400,000 people each year in the United States.[1] Survival rates from cardiac arrest (CA) vary widely[2] but those who do survive are often functionally limited by the neurologic insult from ischemia–reperfusion injury.[3] While there are no specific pharmacologic therapies proven to improve outcomes after cardiac arrest, the use of therapeutic hypothermia has been shown to improve neurologic outcome in this population.[4,5] Side effects of therapeutic hypothermia include an increased risk for arrhythmia, infection or bleeding, and shivering.[6]

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Neuromuscular blockade (NMB) was recently reported to improve outcomes in patients with acute respiratory distress syndrome (ARDS) although this remains controversial.[7] The exact mechanism of this effect has yet to be elucidated but may include reduced oxygen consumption by respiratory muscles, increased arterial oxygenation, or a decrease in patient-ventilator dyssyncrony.[8,9] In post-CA patients receiving therapeutic hypothermia, NMB may be used to prevent shivering, yet the evidence evaluating the use of NMB in post-CA populations is limited.[10] In the two initial randomized trials showing improved outcome with the use of therapeutic hypothermia, NMB was commonly used in the treatment group but not in the placebo group presenting a possible confounding treatment effect.[4,5] Further, the American Heart Association (AHA) has recommended minimizing the use of NMB in post-CA patients or avoiding it altogether.[11] Whether NMB affects outcomes in patients following OHCA is unknown.

Our objective was to evaluate the effect of NMB in OHCA patients following return of spontaneous circulation with the purpose of determining whether there is evidence suggesting a benefit of NMB in this population. Our hypothesis was that NMB in the early post-arrest period would improve overall survival for this population. We utilized data collected in a multi-center prospective observational investigation of adult OHCA to test this hypothesis.

2. Methods

2.1. Design and setting

The National Post-Arrest Research Consortium (NPARC) is a clinical research network conducting research in post-cardiac arrest care. The network consists of four urban tertiary care teaching hospitals and was established to evaluate treatment strategies for individuals who are successfully resuscitated after out-of-hospital cardiac arrest. The current investigation is a *post hoc* analysis of a prospectively conducted NPARC trial evaluating mitochondrial injury in post-cardiac arrest patients (NIH 3UL1RR031990-02S1).

2.2. Study population

The study population of interest consisted of consecutive adult OHCA patients who presented to the Emergency Department (ED) at one of the four NPARC centers during the period from 6/2011 to 3/2012. Potential eligible subjects were identified through automated alerts and electronic notification systems or post-cardiac arrest consultation requests. Trained research assistants were responsible for screening and recruitment. We included patients who were 18 years of age or older who had suffered OHCA with sustained ROSC (defined as the presence of palpable pulses for >20 min) and who were comatose (not following commands) upon presentation to the NPARC hospital. Patients were excluded if they were not comatose following the arrest, if they had blunt or penetrating injury as the primary cause of arrest, if they were pregnant, or if they were prisoners. The study was approved by the Institutional Review Board at each participating site.

2.3. Data collection and data management

Data were abstracted from the EMS reports, ED charts and hospital records using standardized definitions. We collected demographics and other baseline characteristics including initial cardiac arrest rhythm, initial vital signs, and laboratory results. We assessed the presence or absence of bystander cardiopulmonary resuscitation and documented interval from collapse to initiation of CPR and the interval from CPR initiation to return of spontaneous circulation. We recorded pharmacologic interventions including the use of vasoactive agents or neuromuscular blocking agents. Therapeutic hypothermia data and the results of cardiac catheterization procedures were recorded. Vital signs and laboratory data were collected at baseline and every 12 h up to a maximum of 48 h following the arrest. For the analysis of mitochondrial injury in the parent study, blood specimens were collected every 12 h for a maximum of 48 h following the arrest. We computed OHCA scores from initial cardiac arrest rhythm, the intervals collapse-to-CPR and CPR-to-ROSC, baseline creatinine and baseline lactic acid levels.[12] The OHCA score is a prognostic score derived specifically to predict poor neurologic outcome in OHCA populations and we have validated its reliability as a predictive tool in an external population.[13] OHCA scores were treated as a continuous variable for multivariable adjustments. All data were collected locally, removed of any personal identifying information and entered into a secure electronic database that was shared across participating sites. Data were entered and inspected to ensure accuracy and reliability.

2.4. Outcome measures

The primary outcome measures for the parent investigation (NIH 3UL1RR031990-02S1) were levels of circulating markers of mitochondrial injury. For the current analysis, the exposure of interest was NMB for a duration of 24 h following ROSC and the primary outcome was in-hospital survival. We assessed the association between 24 h of NMB and functional status at hospital discharge using the modified Rankin scale.[14] This is a validated scale, ranging from 0 to 6, which is used for measuring the performance of daily activities by patients who have suffered a stroke and is used commonly in cardiac arrest investigations.[15,16] Lower scores represent better performance; scores of 4 or greater represent severe disability or death. For the purposes of this investigation we dichotomized patients into groups for favorable (MR 0–3) or poor functional outcome (MR 4–6), which has been used previously in cardiac arrest investigations.[16] Secondary outcomes were the evolution of oxygenation (PaO_2:FiO_2) over 48 h, and the trend in lactate clearance over 48 h. We chose the ratio of PaO_2:FiO_2 as an endpoint for this analysis as rapid improvement of this variable is associated with better outcomes for patients with ARDS.[17] We chose lactate clearance as an outcome measure as effective lactate clearance has been associated with improved outcomes in OHCA[18–20] as well as other critically ill populations.[21–23]

2.5. Statistical analysis

Baseline characteristics were summarized using simple descriptive statistics including means or medians for continuous data and frequencies with percentages for categorical or discrete variables. For univariate comparisons, we used *t*-test or Wilcoxon rank-sum test for continuous data depending on normality of the data and Chi-square for categorical data. All multivariable models included NMB use for 24-h as the primary explanatory variable of interest. For the identification of relevant confounders for multivariable models we used univariate logistic regression to evaluate the independent association on outcomes for each of the following possible explanatory variables: age in years, subject sex and race, location of arrest (private residence, public space, healthcare facility or other), whether the event was witnessed, presence of bystander CPR, history of co-existing medical conditions (coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, diabetes, hypertension, previous myocardial infarction, liver disease, kidney disease), the use of vasoactive medication upon admission, baseline vital signs (temperature, heart rate, respiratory rate and Glasgow Coma Scale) and baseline laboratory data (white blood cell count, platelets, hematocrit, serum blood glucose, arterial blood pH, PaO_2 and $PaCO_2$), and calculated OHCA

Table 1
Baseline characteristics according to the use or non-use of early, sustained (24 h) neuromuscular blocking agents following CA.

Characteristic	Total $n = 111$	24 h NMB $n = 18$	No NMB $n = 93$	*P*-value
Age	63 (50–75)	56 (48–74)	63 (50–75)	0.7
Female sex (%)	45 (41)	4 (22)	41 (44)	0.1
Race *n* (%)				
Asian	3 (3)	1 (6)	2 (2)	
Black/African–American	36 (32)	6 (33)	30 (32)	0.9
White	67 (60)	10 (56)	57 (61)	
Unknown	5 (5)	1 (6)	1 (6)	
Arrest location *n* (%)				
Private residence	51 (46)	5 (28)	46 (50)	
Public space	28 (25)	7 (38)	21 (23)	0.1
Healthcare facility*	26 (23)	6 (33)	20 (22)	
Other	6 (5)	0 (0)	6 (6)	
Witnessed arrest *n* (%)	89 (80)	17 (94)	72 (77)	0.3
Bystander CPR *n* (%)	41 (37)	7 (39)	34 (37)	0.9
Shockable rhythm *n* (%)	56 (50)	11 (61)	45 (48)	0.4
Collapse-to-ROSC interval (min.)	21 (12–30)	13 (9–25)	22 (13–30)	0.04
Baseline vasopressor use *n* (%)	56 (50)	6 (33)	50 (54)	0.1
Co-morbid conditions *n* (%)				
Coronary artery disease	34 (31)	6 (33)	28 (30)	0.8
Congestive heart failure	12 (11)	4 (22)	8 (9)	0.09
Chronic obstructive pulmonary disease	20 (18)	0 (0)	20 (22)	0.02
Diabetes	35 (32)	4 (22)	31 (33)	0.4
Hypertension	64 (58)	11 (61)	53 (57)	0.7
Previous myocardial infarction	19 (17)	3 (17)	16 (17)	1.0
Vital signs				
Temperature (C)	35.7 (35.3–36.3)	36.1 (35.6–37.0)	35.6 (35.1–36.1)	0.1
Heart rate (bpm)	96 (78–117)	96 (83–116)	91 (77–118)	0.8
Respiratory rate (bpm)	18 (15–21)	18 (15–22)	17 (15–19)	0.4
Mean arterial pressure (mmHg)	131 (113–154)	154 (131–181)	129 (110–148)	0.09
Laboratory data				
White blood cell count ($\times 10^6$)	13 (9.3–18.3)	13.3 (9.2–19.6)	13.0 (9.5–18.0)	0.7
Creatinine ($mmol\,l^{-1}$)	1.2 (1.0–1.7)	1.2 (1.0–1.7)	1.3 (1.0–1.7)	0.5
Glucose ($mg\,dL^{-1}$)	227 (160–278)	187 (154–237)	234 (161–296)	0.2
Blood pH	7.24 (7.14–7.32)	7.30 (7.26–7.36)	7.22 (7.12–7.31)	0.04
INR	1.2 (1.1–1.4)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.3
Lactic acid ($mmol\,l^{-1}$)	5.6 (2.8–9.6)	4.9 (2.2–7.7)	5.7 (3.0–9.9)	0.2
OHCA score	19 (3–34)	8 (0–31)	22 (3–34)	0.2

*Healthcare facility includes ambulance, emergency department, rehabilitation or nursing facility.

score. Variables that were identified to be associated ($p < 0.05$) with outcomes were entered into a stepwise selection procedure with a maintenance criterion of $p = 0.05$ and selected variables were included in the final multivariable logistic models. For the final multivariate model, we used generalized estimating equations to account for clustering effects at the four hospitals. We performed a single sensitivity analysis for the primary outcome forcing OHCA Score into the multivariable model. Secondary outcomes were analyzed using multivariate linear mixed-models for the relationship between NMB and oxygenation or lactic acid levels. All reported confidence intervals are 95% confidence intervals and all tests were two-sided at a 5% significance level. All tests of the data were performed in SAS v. 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients and NMB practice patterns

During the nine-month enrollment period a total of 220 OHCA patients presented to the ED at one of the four NPARC centers; written informed consent was obtained for 111 subjects and were included in this analysis (Fig. 1). The median age was 63 years (IQR: 50–75) and 41% were female. Therapeutic hypothermia was completed in 97% and overall survival was 47%. There were 77 (69%) patients documented to have received NMB at any point within the first 24 h following ROSC. A portion of these patients (18/111, 16%) patients had NMB initiated immediately and sustained for a minimum duration of 24 h following return of circulation.

Compared to those who did not receive sustained NMB, patients with 24-h NMB had shorter intervals from collapse-to-ROSC (13 min [IQR: 9–25] versus 22 min [IQR: 13–30]; $p = 0.04$) and higher baseline blood pH values (pH = 7.30 [IQR: 7.26–7.36] versus 7.22 [IQR: 7.12–7.31]; $p = 0.04$). There was a lower incidence of chronic obstructive pulmonary disease in patients with NMB compared to patients without NMB (0% versus 22%; $p = 0.02$). OHCA prognostic scores were similar between the two groups. Additional characteristics of the cohort are shown in Table 1.

3.2. Association of NMB with outcomes

Overall survival was 52% in patients who received NMB at any point during the initial 24 h following ROSC compared to 35% in patients who received no NMB ($p = 0.1$). Patients with 24 h of NMB had a greater probability of survival compared to patients without 24 h of NMB (78% versus 41%; $p = 0.004$). After multivariable adjustments sustained NMB for 24 h remained independently associated with in-hospital survival (adjusted OR: 7.23, 95% CI: 1.56–33.38). Individual parameter estimates for the primary multivariable model as well as the sensitivity analysis are shown in Table 2. In patients who received 24 h of sustained NMB there was a trend toward favorable functional outcome (MR 0–3) with NMB compared to without NMB, however, this trend did not reach statistical significance (50% versus 28%; $p = 0.07$). Additional outcomes data are shown in Table 3.

There was a significant improvement in lactic acidosis with 24 h NMB in both unadjusted ($p = 0.005$) and adjusted repeated measure analyses (adjusted $p = 0.01$). Fig. 2 shows a comparison of lactate

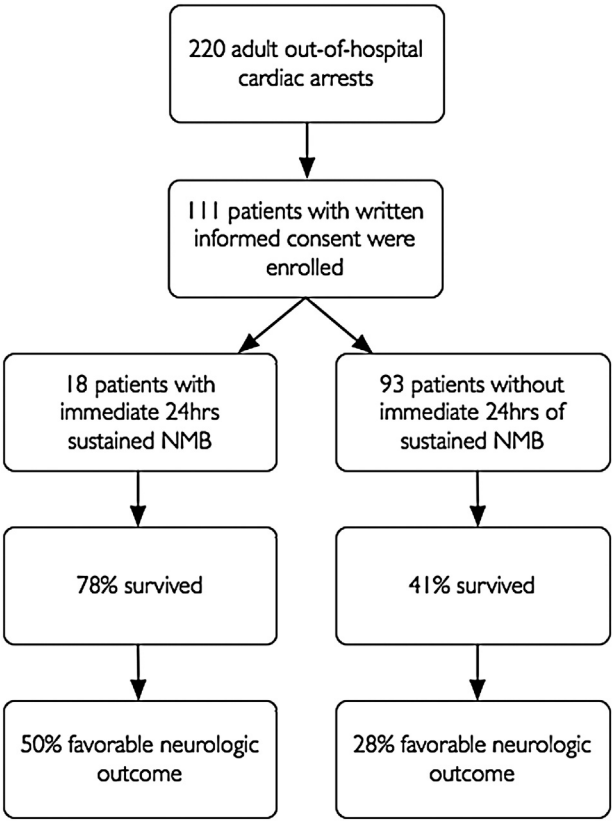

Fig. 1. Flow chart of patient enrollment and exclusion.

Table 2
Multivariable logistic regression for the primary outcome of in-hospital survival. Results of the primary analysis and sensitivity analysis with OHCA score forced into the model are shown.

Variable	Odds ratio (95% CI)	*P*-value
Primary analysis		
24 h NMB	7.23 (1.56–33.38)	0.01
Baseline vasopressor use	0.30 (0.12–0.74)	0.009
INR	0.13 (0.02–0.83)	0.03
Sensitivity analysis		
24 h NMB	7.10 (1.55–32.43)	0.01
Baseline vasopressor use	0.39 (0.15–1.03)	0.06
INR	0.15 (0.03–0.84)	0.03
OHCA score	0.98 (0.95–1.01)	0.14

NMB, neuromuscular blockade; OHCA Score, out-of-hospital cardiac arrest score.

Table 3
Outcomes according to use or non-use of early, sustained NMB in post-CA subjects.

Outcome	Total	24 h NMB	No NMB	*P*-Value
Survivor MV (days)	4 (3–6)	5 (3–6)	4 (2–6)	0.53
Survivor ICU LOS (days)	7 (5–10)	8 (6–8)	6 (4–10)	0.31
Survivor hospital LOS (days)	13 (9–19)	15.5 (11–18)	12.5 (8–20)	0.42
Hospital survival *n* (%)	52 (47)	14 (78)	38 (41)	0.005
Favorable Functional Status (MR[a] 0 – 3) *n* (%)	35 (32)	9 (50)	26 (28)	0.07

MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay; MR, modified rankin.
[a]Modified Rankin Scale[14]. 0, no symptoms at all; 1, no significant disability despite symptoms; able to carry out all usual duties and activities; 2, slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3, moderate disability requiring some help, but able to walk without assistance; 4, moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5, severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6, Death.

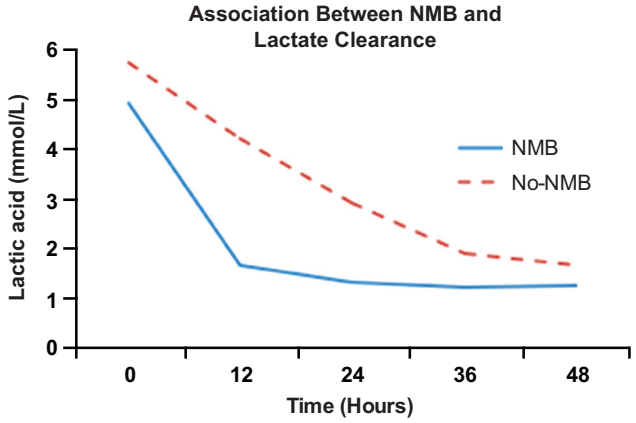

Fig. 2. Change in lactic acid levels between subjects with early, sustained NMB use versus patients without sustained NMB use.

clearance between the two groups. Individual comparisons of lactic acid level revealed a lower lactic acid level in patients with NMB at 12 h (1.7 [IQR: 1.1–2.6] versus 4.1 [IQR: 2.1–6.5]; $p < 0.001$) and 24 h (1.3 [IQR: 0.9–2.0] versus 2.9 [IQR: 1.5–5.5]; $p < 0.001$). At 36 h and 48 h there was no difference in lactic acid level between the two groups (36 h: 1.2 [IQR: 1.1–2.2] versus 1.9 [IQR: 1.2–2.8]; $p = 0.1$; 48 h: 1.3 [IQR: 1.1–2.6] versus 1.7 [IQR: 1.3–2.6]; $p = 0.4$). There were 36 (32%) patients who had PaO_2:FiO_2 > 300 immediately following ROSC, 14 (13%) patients with PaO_2:FiO_2 < 300 suggesting acute lung injury, and 38 (34%) patients who had a PaO_2:FiO_2 < 200 making criteria for Acute Respiratory Distress Syndrome immediately following ROSC. There were missing oxygenation data 23 (21%) subjects at baseline at subsequent follow-up time points (12 h: 13%, 24 h: 18%, 36 h: 23%, and 48 h: 30%). There was no significant difference in baseline PaO_2:FiO_2 values (no-NMB, 230 [IQR: 107–465] versus NMB, 412 [IQR: 170–746]; $p = 0.3$). There was no effect of NMB on the evolution of PaO_2:FiO_2 ($p = 0.5$) and there were no significant differences in PaO_2:FiO_2 at any of the follow-up time points (12 h: no NMB, 303 [IQR: 176–468] versus NMB, 396 [IQR: 240–495], $p = 0.4$; 24 h: no-NMB, 326 [IQR: 208–452] versus NMB, 320 [IQR: 245–454], $p = 0.9$; 36 h: no-NMB, 330 [IQR: 218–443] versus NMB, 306 [IQR: 211–485], $p = 0.9$; 48 h: no-NMB, 278 [IQR: 205–421] versus NMB, 270 [IQR: 184–394], $p = 0.6$).

4. Discussion

In this multicenter investigation of adult OHCA we found that NMB in the post-CA period is common as the majority of these patients received NMB at some point in the 24 h following ROSC. However, only a fraction of patients (16%) received NMB for a sustained 24-h period. We found that compared to patients who do not receive early, sustained NMB, patients with 24 h of NMB had improved survival as well as improved lactic acid clearance. These associations remained significant after multivariate adjustments for confounders suggesting that early, sustained NMB may affect outcomes from OHCA.

Our hypothesis that NMB could affect outcomes from OHCA is based on the concept that NMB may reduce global oxygen consumption and metabolic demand as well as an improvement in pulmonary gas exchange. Further, NMB use in the post-arrest period may also prevent patients from ventilator dyssynchrony, a periodic occurrence which may result in episodes of increased intracranial pressure. Our findings are consistent with the results of previous investigations that have demonstrated improved outcomes with NMB in other critically ill populations. Specifically, in a large randomized trial of NMB versus placebo, Papazian et al. demonstrated improved long-term survival benefit with early, sustained

NMB for patients with acute respiratory distress syndrome without increasing the incidence of ICU-acquired paresis.[7] The authors hypothesized that NMB would improve outcome through improved pulmonary gas exchange and found that a continuous 48-h infusion of cisatracurium improved adjusted survival rate and the total number of ventilator-free days in patients with ARDS. We evaluated OHCA patients regardless of their presenting respiratory status and we were unable to detect any differences in the evolution of oxygenation between patients treated with sustained NMB compared to those without. However, a significant proportion (21%) of baseline respiratory data was missing in this study.

In the context of therapeutic hypothermia having become the standard of care for post-arrest patients, NMB practice patterns in this population may be changing as clinicians attempt to prevent patients from shivering, a common side-effect of the hypothermia protocol. Further, hypothermia protocols differ between hospital systems with some seeking to avoid NMB and others employing them routinely for the entire hypothermic period. The AHA evaluated the use of NMB in the 2010 AHA ACLS guidelines and concluded that they may be necessary at times but use should be limited as they could be potentially harmful.[11] However, these conclusions were drawn from expert opinion and extrapolation of other studies and prior to the recently published data in ARDS. In addition, despite the research and use of NMB in other critical illnesses such as ARDS, there is a paucity of data to guide NMB specifically in post-CA patients.[24,25] To the best of our knowledge, this is the first report to investigate any potential benefit of NMB in a population of OHCA.

Effective lactate clearance has been shown previously to be an important indicator of prognosis in critical illnesses[21–23] and has also been associated with improved survival in cardiac arrest populations.[18–20] Our finding that early, sustained NMB is associated with reduced blood lactate concentrations is novel in that we are unaware of any previous report that describes an association of NMB on lactic acid production or clearance. Elevated lactic acid levels in the post-arrest period most likely represent impaired tissue perfusion and a high level of metabolic activity but it is also possible that post-arrest patients undergoing hypothermia have some level of shivering which could cause an increase in lactic acid levels. Although we are unable to identify the exact mechanism for this result NMB may act prominently to prevent shivering and may have secondary effects to reduce cerebral and overall metabolic demand.[26] Future investigations are necessary to confirm our findings and to elucidate the precise mechanism of this effect.

Our finding that early, sustained NMB is associated with improved survival raises important questions about the interpretation of results of previous investigations demonstrating improved outcomes from cardiac arrest with a period of therapeutic hypothermia. Two randomized trials in OHCA patients with initial shockable cardiac arrest rhythms demonstrated improved neurologic outcomes with a protocol of sustained hypothermia.[4,5] These findings have been supported by the results of other investigations using historical controls[27,28] and as a result, therapeutic hypothermia has become the standard of care for post-arrest populations.[11] However, the potential confounding from use of NMB in the hypothermia group in the two initial randomized trials has not been considered previously. Specifically, whereas patients who were randomized into the normothermia (37 °C) treatment arms received small doses of a neuromuscular blocking agent only during the induction period of temperature management, patients who were randomized into the hypothermia arms received as needed small doses of neuromuscular blocking agent (vecuronium or pancuronium) to prevent shivering during the active cooling period as well as during the period of re-warming. Thus, the possibility remains that patients in the hypothermia arms of these studies had a higher rate of shivering and therefore received NMB boluses more frequently than the patients in the normothermia groups.

Our findings raise many questions in addition to those concerning the potential interaction between NMB and therapeutic hypothermia. Specifically, there is no guidance or known optimal duration of NMB following OHCA. For the current investigation we chose to investigate the effect of NMB in the 24 h immediately following ROSC as the primary exposure of interest as this is the expected duration of therapeutic hypothermia for post-CA patients and is the period with the highest likelihood for NMB administration. In this cohort of patients we observed a high rate (97%) of therapeutic hypothermia and whether the associations of NMB on outcomes are an adjunctive effect of NMB during therapeutic hypothermia or if NMB functions independent of core body cooling remain unknown. Several studies have suggested that long-term administration of NMB may be associated with the development of critical illness polyneuropathy or generalized muscle weakness following critical illness.[29,30] We did not specifically investigate the incidence of muscle weakness and it is possible that NMB increases the incidence of muscular weakness in this population. Additional studies are required to evaluate the safety of NMB during the immediate post-CA period and to evaluate their effect on possible long-term polyneuropathy. An important limitation of this observational study is the uncertainty about why NMB was used in certain patients. It is possible that patients with more intact reflexes, shivering or spontaneous movement were more likely to receive NMB than patients with less vigorous neurological examinations. Thus, the possibility remains that patients without sustained NMB were less responsive (i.e., worse neurological status) and therefore did not clinically require continued therapy therefore creating selection bias. Finally, whether heavy sedation in the post-CA period would confer similar results is possible but has yet to be explored.

The strengths of this study include the prospective multicenter design and use of standard data collection and data management tool. We enrolled consecutive adult OHCA patients presenting to the EDs at the four NPARC centers and patients were only included if they were comatose immediately following ROSC making the results generalizable more broadly to other OHCA populations. A number of limitations must be considered when interpreting the results of this investigation. First, this is a *post hoc* analysis and data were not collected specifically for the question of interest in the current study and the possibility remains that data collection errors have occurred. However, we attempted to minimize this limitation through the use of standardized definitions for data collection and data were entered into a single electronic database and inspected for reliability. Second, this is an observational study and we cannot assess a causal relationship between the primary exposure and outcomes. We attempted to overcome this limitation through multivariable adjustments for potential confounding of the results but it is possible that unmeasured confounding remains. Third, we are unable to ascertain the exact clinical indications for NMB in this cohort of patients and for this reason we cannot eliminate the possibility of confounding from clinician treatment bias. For example, the shorter collapse-to-ROSC interval and higher pH in patients who received sustained NMB compared to patients without sustained NMB may reflect the fact that these patients demonstrated some movement or activity suggestive of favorable neurologic status at the time of hospital arrival. However, it is also possible that patients who received NMB demonstrated myoclonus (which is typically associated with worse outcomes in this population) and required NMB to prevent myoclonus. Additional studies are necessary to elucidate specific reasons for NMB in this population of patients. Finally, for our secondary outcome for the evolution of respiratory status we had a proportion of missing data at all time points.

5. Conclusion

In this population of OHCA, we found that early NMB that is sustained for a 24-h period is associated with an increased probability of survival. Secondarily, we found that early, sustained NMB is associated with improved lactate clearance. The administration of NMB in the early post-CA period may improve outcomes, however, clinical trials are necessary to assess any causal relationship between NMB and outcome from OHCA.

Conflict of interest

Joseph P. Ornato – Co-Chair, NIH-sponsored Resuscitation Outcomes Consortium (ROC), Benjamin S. Abella – Philips Healthcare, NIH, Medtronic Foundation, Doris Duke, HeartSine, Velomedix, David F. Gaieski – Stryker Medical and rest of the authors have no conflict of interest.

Competing interests

The authors state that they have no competing interests.

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