Variation in sedation and neuromuscular blockade regimens on outcome after cardiac arrest

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Abstract

Objective—Sedation and neuromuscular blockade (NMB) protocols in patients undergoing targeted temperature management (TTM) after cardiac arrest address patient discomfort and manage shivering. These protocols vary widely between centers and may affect outcomes.

Design—Consecutive patients admitted to 20 centers after resuscitation from cardiac arrest were prospectively entered into the International Cardiac Arrest Registry between 2006–2016. Additional data about each center's sedation and shivering management practice was obtained via

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survey. Sedation and shivering practices (SP) were categorized as escalating doses of sedation and minimal or no NMB (SP1), sedation with continuous or scheduled NMB (SP2), or sedation with as-needed NMB (SP3). Good outcome was defined as cerebral performance category (CPC) score of 1 or 2. A logistic regression hierarchical model was created with two levels (patient-level data with standard confounders at level one and hospitals at level two) and sedation practice as a fixed effect at the hospital level. The primary outcome was dichotomized CPC at 6 months.

Setting—Cardiac arrest receiving centers in Europe and the United states from 2006–2016

Patients—Four thousand two hundred sixty seven cardiac arrest patients 18 years or older enrolled in the International Cardiac Arrest Registry.

Interventions—None

Measurements and Main Results—The mean age was 62±15 years, 36% were female, 77% out-of-hospital arrests, and mean ischemic time was 24(±18) minutes. Adjusted odds ratio (for age, return of spontaneous circulation, location of arrest, witnessed, initial rhythm, bystander CPR, and defibrillation, medical history country and size of hospital) was 1.13 (0.74–1.73, p=0.56) and 1.45 (1.00–2.13, p=0.046) for SP2 and SP3 respectively, referenced to SP1.

Discussion—Cardiac arrest patients treated at centers using as-needed NMB had increased odds of good outcomes compared to centers using escalating sedation doses and avoidance of NMB, after adjusting for potential confounders. These findings should be further investigated in prospective studies.

Introduction

Targeted temperature management (TTM) may improve functional outcomes of patients with hypoxic ischemic encephalopathy (HIE) after cardiac arrest, and is recommended for these patients after the return of spontaneous circulation (ROSC)(1). Sedative and analgesic infusions and neuromuscular blockade agents (NMB) are commonly used during TTM for comfort, suppression of shivering, and reduction of metabolic activity, but the optimal regimens are unknown, and dosing strategies vary widely(2–5). During TTM, shivering increases the systemic metabolic rate(6), reduces brain oxygen levels(7), and increases intracranial pressure(8), and cause variability in body temperature, each of which can worsen secondary neurologic injury. To counteract these effects, different strategies have been proposed, ranging from high dose of sedatives and analgesics without NMB, to much lower dose with intermittent or continuous NMB(2, 9, 10).

Deeper sedation is associated with worse outcomes in other medical and surgical ICU populations (8, 11–15). During TTM, observational studies suggest that sedatives and analgesics accumulate due to impaired metabolism, which can delay wakening, confound neurologic assessment, and potentially result in inappropriate withdrawal of life support(4, 9, 16–18). Deeper sedation also may induce more hypotension with or without lower cardiac index, which may also affect outcomes (19–22). The approach to NMB during TTM also

varies widely, from recommendations to avoid its use, to observational data that continuous use may improve outcome after cardiac arrest(2, 4, 9, 10, 23–25). For these reasons, optimization of sedation is thought to be essential in the management of patients with critical illness(26), and the specific effects of sedation on cardiac arrest survivors undergoing TTM could be profound, but are unknown.

Current literature available to address this issue has used single-center data to associate NMB dosing to outcome, however has likely not appropriately adjusted for underlying severity of illness and is complicated by patients with very severe brain injury having less shivering. The only randomized trial comparing continuous versus as needed NMB dosing protcolized the as needed group to escalating doses of sedation as well, making the results difficult to interpret. To address these controversies and inconsistencies, we evaluated sedation and shivering management practices in the International Cardiac Arrest Registry (INTCAR), a multicenter registry of patients that have been successfully resuscitated after in-hospital and out-of-hospital cardiac arrests.

Materials and Methods

Centers and Patients

We included centers participating in the INTCAR registry between 2006 and 2017. The INTCAR registry consists of two iterations: a 1.0 dataset between the years of 2006–2011 and a 2.0 dataset between the years of 2011–2017. The core common variables of this retrospective data set were merged for this analysis. Centers enrolled consecutive adult patients admitted to an intensive care unit after in-hospital or out-of-hospital cardiac arrest. Only patients treated with TTM were included, and management varied according to local best practices. The database was maintained at Lund, Sweden on the Lytics© server. Centers participated in the registry on a volunteer basis, and there was no reimbursement for enrolling patients, and all had institutional review board approval at their center. The merging of the 1.0 and 2.0 iteration and the analysis below was competed in R software version 1.0.136(27).

Sedation Practices

Patient-level sedation data was not part of the INTCAR database. Center-specific sedation practices (SP) were assessed using a Research Electronic Data Capture (REDCap) based survey hosted at Tufts University(28). Surveys were sent by email to the investigators listed in the INTCAR system up to three times, on different days of the week. Centers that did not respond were then contacted directly by the administrators of INTCAR and asked to complete the survey. Two investigators independently assigned centers into one of the three categories based on their survey results: SP1 indicated escalating sedation dosing and avoidance of NMB, SP2 indicated sedation with either scheduled or continuous NMB to prevent shivering, and SP3 indicated sedation with as-needed NMB in response to shivering. Only centers that enrolled at least 20 patients and completed the survey were included in the analysis.

Outcome

The primary outcome was CPC at 6-month as a dichotomous variable, with good outcome defined as CPC of 1 or 2 and poor outcome as CPC of 3–5. Secondary outcome was CPC at ICU discharge. The 6-month CPC outcome was assessed with a review of medical records or telephone call to the patient or their proxy.

Predictors

Candidate variables included in both INTCAR iterations were age, sex, number of prior medical conditions (CAD, CHF, arrhythmia, COPD, hypertension, CKD, neurologic disease, liver disease, malignancy, obesity, IDDM and NIDDM), ischemic time, location of arrest (in hospital vs. out-of-hospital), rhythm (shockable, non-shockable, and unknown), bystander CPR, witnessed CPR, number of beds at each center and country of center (European versus United States). These were extracted by chart review at the individual centers and uploaded into the Lytics© server. Continuous variables were tested for linearity assumptions.

Missing data

Missing data was assessed and those with variables with greater than 10% missing data were estimated with multiple imputation. The imputation method was predictive mean metric, where 5 coefficients are assigned for each missing data point based on closest matches with complete data, then randomly samples of the donors are randomly selected and the observed value is returned. This was repeated 10 times and results pooled for the multivariate imputation by chained equations (mice) analysis. (29)

Statistical analysis methods

Predictors were separated into patient-level and center-level sets. To account for shared variance between center, sedation use, and patient use, a hierarchical model was used with two levels (patients at level one and centers at level two) with sedation practice as a fixed effect at center level. Explanatory variables were largely treated as dichotomous for yes/no variables and continuous variables were assessed for linearity with the logit of the outcome variables. Age was grouped by decade and ROSC was grouped by 5-minute intervals. Past medical history consisted of a sum of relevant pre-arrest diagnoses listed above. Candidate variables were assessed in a univariate manner using logistic regression and variables were retained in the model if the p-value was < 0.20. The decision was made a-priori to force certain selected variables into the model, regardless of significance based on clinical importance (ROSC, rhythm, location, bystander CPR).

Results

Survey

Thirty five eligible INTCAR centers were sent surveys, and 20 (57%) responded. Each center was assigned to one of the three categories based on their survey results without discrepancy between the assigners.

Patient population

A total of 4,267 patients at 20 centers were included in the dataset. The mean age was 62 (± 15) years, 34% (n= 1432) were female and 77% (n=3256) were out of hospital arrests. There were similar rates of shockable and non-shockable rhythms and mean ischemic time was 24 (± 18) minutes. Further characteristics, including characteristics from the complete INTCAR dataset, are described in Table 1. At 6 month follow-up 1,349 (32%) had a good outcome, with similar results at ICU discharge (1,313 (31%)).

Missing data

At least one variable was missing from 23% of patients. 11% of patients had more than one variable of missing data. The most common variable with missing data was bystander CPR. Multiple imputation was performed with 5 imputations and pooled for the final analysis.

Model development

Variables were selected a priori from existing literature describing outcome prediction after cardiac arrest. The results of univariate analyses are shown in Supplement table 1–2. Age and ROSC were changed from continuous variables to intervals due to the nonlinear relationship of the raw variables with the outcome variables (Supplement figure 1,2). After model development, a priori interactions were tested and not found to be significant. All univariate variables were found to be significant and were retained in the model. First, the global p value for sedation level for each outcome was tested, followed by testing the three sedation practices referenced to sedation practice 1.

Model specification

The full model is shown in Supplementary Table 1. Variables retained in the model included age, sex, arrest location, medical history, ischemic time, witnessed arrest, bystander CPR, rhythm, country, defibrillation, and hospital size.

Outcome by sedation category

For the primary outcome of 6-month CPC referenced to SP1, the global p-value was significant at 0.003. The unadjusted odds ratios for good outcome were 1.19 (0.88–1.42, p=0.07) for SP2 and 1.65 (1.40–1.97, p<0.001) for SP3. The adjusted odds ratios were 1.13 (0.74–1.73, p=0.56) for SP2 and 1.45 (1.00–2.13, p=0.046) for SP3. For the secondary endpoint of dichotomized ICU discharge CPC, the global p-value was significant at 0.002. The unadjusted odds ratios for good outcome were 1.10 (0.90–1.34, p=0.34) for SP2 and 1.69 (1.41–2.01, p<0.001) for SP3, and the adjusted odds ratio was 0.86 (0.55–1.35, p=0.52) for SP2 and 1.46 (0.97–2.20, p=0.07) for SP3, all referenced to SP1.

Discussion

In patients receiving TTM after cardiac arrest, improved functional outcomes was associated with patients admitted to centers that used as-needed NMB with an adjunctive sedation regimen compared to centers using escalating sedation dosing and limiting NMB, including

after adjustment for major confounders. This is the largest study to evaluate the impact of sedation and NMB on outcomes after cardiac arrest.

Current guidelines recommend "light" sedation (i.e. awake and responsive) in the general ICU population, which is associated with improved outcomes(13, 30), but applying this approach to cardiac arrest patients undergoing TTM is inappropriate. Monitoring the depth of sedation has not been validated in brain-injured patients, as mental status changes may be secondary to brain injury rather than sedation.

In addition to inconsistent sedation strategies during TTM, the use of NMB varies widely, and the benefits or risks are uncertain. A recent guideline for the use of NMB in the ICU made no recommendation regarding the use of NMB during TTM(31). Several observational TTM studies have concluded that NMB administration was associated with improved outcome (23–25) although these studies did not robustly adjust for underlying severity of illness. Some experts have recommended avoiding NMB during TTM(1, 10). Shivering itself is associated with good outcome after cardiac arrest,(33) possibly because the most severely injured brains do not mount a shivering response. Therefore requiring treatment for shivering with NMB may reflect a less severe brain injury and thus explain the association with better outcome. The most recent study was a single center study of 63 randomized continuous versus as needed NMB. This studies positive finding was fewer shivering episodes in the continuous NMB group. Secondary outcomes showed lower doses of sedatives and analgesics, decreased length of ICU stay and earlier awakening in the continuous NMB group. However, it is important to note that patients received escalating doses of sedatives and analgesics with each dose of rocuronioum per protocol(32). Therefore, it is unclear if the time to awakening and ICU stay is reflective of the NMB practice or the protocol of increasing sedation and analgesia in the as needed NMB group. Our analysis, where sedation and shivering strategies were defined at the hospital level, avoids this within-patient confounder and may be more generalizable to a center-treatment approach.

Worse outcomes associated with escalating sedation dosing sedation after cardiac arrest has several plausible explanations. The metabolism of many sedatives and analgesics decreases during hypothermia (34, 35),(16) likely resulting in accumulation of medication, which can confound neuroprognostication after cooling, resulting in inappropriate withdrawal of life support. Targeting a moderate depth of sedation and using NMB to treat shivering reduces the overall dose of sedatives, particularly for those who shiver vigorously, and appears to reduce the time to wakening after TTM. (4, 36) Higher-doses of sedation to control shivering without NNB may also reduce blood pressure, known to influence outcome in animal cardiac arrest models(37, 38) and retrospective human studies.(20, 39) In addition, escalating doses of sedation without NMB may incompletely control shivering, increase variability in body temperature or delay adequate suppression of shivering. Excess shivering has the potential to delay time to target temperature, elevate intracranial pressure, and lower brain oxygen levels. Sedation also has immunology effects,(40, 41) which may increase the rate of infection, time on the ventilator, and prolong ICU course.(2, 13). Lastly, improved outcome with as-needed doses of NMB may be a reflection of increased bedside monitoring of patients.

Although this is the largest study to evaluate the effects of sedation on outcomes after cardiac arrest, several limitations warrant discussion. The INTCAR data were collected prospectively, but sedation and NMB doses were not collected at the patient level. However, every center had a sedation protocol, and although between-patient variability occurs within each center, centers with established protocols may have less drastically divergent variations in treatment sufficient to confound these results. Also centers who choose to participate in INTCAR have a particular interest in post-resuscitation care and it is unclear how these results apply to other centers. Next, the effect of similar sedation approaches within each center may not be consistent across all patients. It is also possible that these effects on outcome may be due to variation in sedation protocols or from other unmeasured differences in practice, such as increased bedside attentiveness with as-needed NMB protocols. Also it should be noted that the groups were not comparable for several variables known to influence outcomes after cardiac arrest, however we used the preferred statistical method of hierarchal logistic regression to minimize bias between these groups. Also, it is possible that the sedation practice could have changed significantly over the course of the study. The survey attempted to address this, asking if and how practices changed after the year 2012 (start of INTCAR 2.0). Fifty percent of centers reported a significant change in their protocol however citing reasons would not have altered their SP category (ie changing from fentanyl to remifentanyl or inclusion of dexmedetomidine). There were two centers that responded that there was a significant change in their protocol but did not explain what that was. One of these centers included patients in both 1.0 and 2.0 datasets and 170 patients were in the 1.0 dataset, and could have been inappropriately assigned.

Protocols for sedation and shivering management of patients undergoing TTM are variable (TTM) and the only randomized trial to address this is difficult to interpret differences in NMB dosing or sedation dosing as an influence to outcome. Our data suggest that good outcome is associated with the use of a protocol that favors as needed NMB with basal sedation instead of increasing sedation to avoid NMB in response to shivering after cardiac arrest. Prospective study evaluating sedative and NMB use at the patient level, with outcomes adjusted for severity of illness, is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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OR for good outcome at follow-up

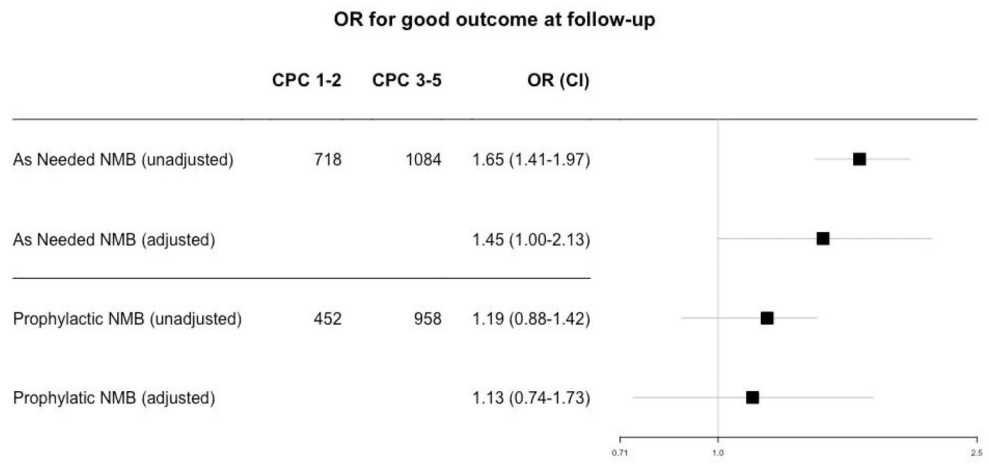|	CPC 1-2	CPC 3-5	OR (CI)
As Needed NMB (unadjusted)	718	1084	1.65 (1.41-1.97)
As Needed NMB (adjusted)			1.45 (1.00-2.13)
Prophylactic NMB (unadjusted)	452	958	1.19 (0.88-1.42)
Prophylatic NMB (adjusted)			1.13 (0.74-1.73)

Figure 1.
Odds ratio for good outcome at s of SP2 (prophylactic NMB) and SP3 (as needed NMB) referenced to SP1 (avoiding NMB).
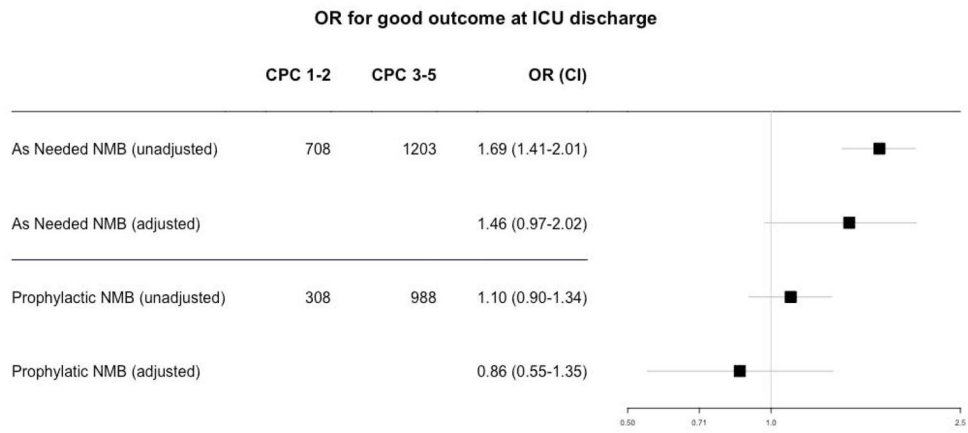CPC: Cerebral Performance Category

OR for good outcome at ICU discharge

	CPC 1-2	CPC 3-5	OR (CI)
As Needed NMB (unadjusted)	708	1203	1.69 (1.41-2.01)
As Needed NMB (adjusted)			1.46 (0.97-2.02)
Prophylactic NMB (unadjusted)	308	988	1.10 (0.90-1.34)
Prophylatic NMB (adjusted)			0.86 (0.55-1.35)

Figure 2.
Odds ratio for good outcome at ICU discharge of SP2 (prophylactic NMB) and SP3 (as needed NMB) referenced to SP1 (avoiding NMB).
CPC: Cerebral Performance Category

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Table 1

Demographics and Clinical Characteristics of All Cardiac Arrest Patients and by Sedation and Shivering Practices

Demographics and Clinical Factors	All INTCAR Centers	All Centers included in analysis	SP1	SP2	SP3
Centers (n,%)	35	20	6, 30	6, 30	8, 40
Number of Patients (n,%)	5450	4267	889, 21	1462, 34	1916, 45
Age (mean, SD)	62.0, 15	61.8, 15	65.4, 16	60.2, 15	61.2, 15
Female (n,%)	1792 (33)	1432 (34)	334, 38	509, 35	589, 30
Medical History Diagnosis (n, IQR)	2 1,3	2 2,2	2 2,2	2 2,2	2 2,2.25
Out-of-hospital (n,%)	4125, 76	3256, 77	634, 72	1183, 81	1439, 75
Witnessed (n,%)	4429, 82	3429, 81	710, 81	1161, 80	1558, 82
Rhythm: PEA/Asystole (n,%)	2478, 49	2050, 50	501, 60	675, 48	874, 47
Shockable (n,%)	2565, 49	1999, 49	320, 39	728, 51	951, 51
Unknown (n,%)	130, 2	64, 2	10, 1	15, 1	39, 2
Time to ROSC (mean, SD)	24, 18	24, 18	23, 18	26, 22	22, 15
Bystander CPR (n,%)	3718, 68	2008, 59	271, 57	715, 60	922, 60
Defibrillation (n,%)	3173, 59	2452, 59	422, 49	877, 61	1153, 61
European (n,%)	2449, 45	1365, 32	475, 53	245, 17	645, 34
ICU CPC1–2 (n, %)	1770, 32	1313, 32	225, 27	380, 28	780, 37
6 month CPC 1–2	1674, 31	1394, 35	224, 28	452, 32	718, 40

PEA: Pulseless electrical activity

VT/VF: ventricular fibrillation/ventricular tachycardia

ROSC: Return of spontaneous circulation

SP: Sedation and shivering practice