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Clinical paper

Continuous versus intermittent neuromuscular blockade in patients during targeted temperature management after resuscitation from cardiac arrest—A randomized, double blinded, double dummy, clinical trial☆

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ABSTRACT

Aim of the study: Current guidelines recommend targeted temperature management to improve neurological outcome after cardiac arrest. Evidence regarding an ideal sedative/analgesic regimen including skeletal muscle paralysis is limited.

Methods: Patients were randomized to either a continuous administration of rocuronium (continuous-NMB-group) or to a continuous administration of saline supplemented by rocuronium bolus administration if demanded (bolus-NMB-group).

The primary outcome was the number of shivering episodes. Secondary outcomes included survival and neurological status one year after cardiac arrest, time to awakening, length of stay as well as required cumulative dose of rocuronium, midazolam and fentanyl.

Results: Sixty-three patients (32 continuous-NMB-group; 31 bolus-NMB-group) were enrolled. Differences in baseline characteristics were not significant. Shivering episodes were detected in 94% of the patients in the bolus-NMB-group compared to 25% of the patients receiving continuous rocuronium infusion ($p < 0.01$). The continuous-NMB-group received significant lower doses of midazolam (4.3 ± 0.8 mg/kg vs. 5.1 ± 0.9 mg/kg, $p < 0.01$) and fentanyl (62 ± 14 μg/kg vs. 71 ± 7 μg/kg, $p < 0.01$), but higher cumulative doses of rocuronium (7.8 ± 1.8 mg/kg vs. 2.3 ± 1.6 mg/kg, $p < 0.01$). Earlier awakening (2 [IQR 2;3] vs. 4 [IQR 2;7.5] days, $p = 0.04$) and decreased length of stay at the ICU (6 [IQR 3;5.9] vs. 10 [IQR 5;15] days, $p = 0.03$) were observed in the continuous-NMB-group. There were no significant differences in survival and quality of life 12 months after cardiac arrest.

Conclusions: Continuous neuromuscular blockade during the first day after resuscitation reduced shivering, midazolam and fentanyl requirement, time to awakening and discharge from intensive care unit. There were no differences in overall survival, cooling rate and time to target temperature.

Introduction

Many patients resuscitated initially from out-of-hospital cardiac arrest (OHCA) suffer from post cardiac arrest syndrome, which could lead to a deterioration of prognosis, especially of neurologic outcome [1]. Targeted temperature management (TTM) has shown to improve neurologic recovery and survival in comatose survivors of OHCA [2].

Although the optimal temperature level of TTM is not defined yet, current resuscitation guidelines recommend to maintain a constant target temperature between 32 °C and 36 °C [3,4].

Sedation and analgesia are required in order to initiate and maintain TTM. Until now, no specific sedation and analgesia protocol is recommended by the guidelines. A continuous administration

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of propofol or benzodiazepines in combination with morphine is commonly used [3–5]. Continuous lowering of body temperature during TTM could lead to shivering, increased oxygen consumption, an increase in heart rate, and a general stress-like response with increased metabolic demands. These effects could counteract the effects of TTM [6,7]. To avoid shivering, the additional administration of neuromuscular blockers (NMB) is often used [5].

Some studies reported an increased probability of survival using NMB for 24–48 h in patients after cardiac arrest and adult respiratory syndrome [8,9].

Conversely, NMB have been associated with the occurrence of critical illness polyneuropathy and myopathy during and after intensive care [10]. Therefore recommendations suggest to minimize or avoid the use of NMB after OHCA [11], even if evidence regarding an ideal sedative/analgesic regimen including skeletal muscle paralysis is limited and subject to interpretation [12,13].

Thus, we have compared a continuous administration of NMB to a demand-oriented strategy in a randomized, controlled trial.

Methods

This trial was performed as a randomized, double blinded, double dummy study. The study was conducted in accordance with local law and the principles of the declaration of Helsinki (Version 2008) and was approved by the local ethical review board (ethical committee number: 253/2009). The requirement of informed consent at the time of inclusion into the study was waived in accordance with the guidelines of good clinical practice and Austrian laws and regulations. In case of survival and favourable outcome the participant was asked to provide written informed consent.

Population

Eligible were all adult patients, older than 18 years, admitted to the Department of Emergency Medicine, Medical University of Vienna, resuscitated from non-traumatic OHCA within six hours prior to arrival at the emergency department. Cardiac arrest had to be of presumed cardiopulmonary origin and patients had to be eligible to receive targeted temperature management. Core body temperature had to be equal or above 35 °C at hospital admission. Patients were excluded in the event of known terminal illness, obvious intoxication, ward of the state or prisoners, or women with known or clinically apparent pregnancy. Patients with known allergic reaction against rocuronium, history of myasthenia gravis or known epileptic disease were excluded as well.

Exposure

The exposure of interest was continuous or on demand NMB application during TTM. Patients randomized to the continuous-NMB-group received rocuronium with an initial bolus of 0.25 mg/kg of bodyweight followed by a continuous application of 0.25 mg/kg/h. Patients in the bolus-NMB-group received an initial bolus of saline as well as a subsequent continuous application of saline. In addition, if shivering was noticed, patients received either a bolus of saline in the continuous-NMB-group or a bolus of rocuronium with 0.25 mg/kg in the bolus-NMB-group.

Sedation was induced by the intravenous administration of midazolam (0.125 mg/kg/h) and fentanyl (2 μg/kg/h). An additional bolus of sedative was allowed, if clinically indicated. The severity of shivering was measured and documented by the attending nurse using the 'Shivering Assessment Scale' (SAS) [14]. If shivering (SAS ≥ 1) was detected, a blinded bolus medication was administered and sedation was increased as an equivalent of an additional bodyweight of 5 kg (accordingly by an increase of midazolam of 0.625 mg/h and of fentanyl of 10 μg/h). The study medication was stopped at 29 h and the sedation and analgesia at 31 h after initiation of cooling (Fig. 1).

Outcome

The primary outcome parameter was the number of shivering episodes during TTM. Secondary outcomes included the cumulative administered dose of each of rocuronium, midazolam and fentanyl; survival and neurologic outcome one year after the initial event. Cooling effort, time to awakening and the length of intensive care unit stay were also recorded. Furthermore, the incidence of critical illness polyneuropathy/myopathy was assessed as secondary tertiary outcome.

Randomization

Treatment assignments were randomly generated by computer and sealed envelopes were produced. Immediately after a patient was enrolled in the study, a sealed envelope was opened by a nurse, who was not involved in the study procedures and the patients' treatment and the patient was assigned to the specific group. This nurse prepared the blinded anti-shivering continuous and bolus medication (NMB or saline).

Treatment

After return of spontaneous circulation (ROSC), and prior to enrolment in this trial, all patients were treated by the emergency medical team on scene according to current guidelines. The initiation of out-of-hospital TTM (via surface cooling and/or cold saline) as well as the administration of an NMB prior to hospital admission was at the discretion of the attending emergency physician on scene. After hospital admission, patients were stabilized according to their clinical state. Arterial saturation was kept >95%; ventilation was set to maintain a partial pressure of CO_2 between 35 and 45 mmHg. Mean arterial blood pressure was kept >60 mmHg using crystalloid fluids and if necessary vasopressor support. Serum blood glucose was kept between 110 and 180 mg/dl.

All patients underwent TTM utilized by an endovascular approach with the cooling catheter advanced into the inferior vena cava via femoral puncture (Thermogard XP®, Quattro catheter; Zoll Medical Corporation, USA). Cooling rate was set to maximum until the target core temperature measured in the oesophagus of 33 °C was reached. The cooling period lasted 24 h from initiation of cooling until the start of rewarming. Then rewarming was performed with a rate of 0.4 °C/h until a core temperature of 36 °C was reached.

Data acquisition and documentation

Acquisition and documentation of data on cardiac arrest were in accordance to the Utstein criteria [15]. Temperature on admission was measured with an infrared tympanic thermometer (Ototemp LighTouch®, Exergen Corporation, MA, USA). An oesophageal temperature probe (Mon-a-therm® General Purpose, 12 french, Mallinckrodt Medical Inc., St. Louis, MO, USA) was used as the main temperature site for regulation of the cooling device. Additionally, a urine bladder temperature probe (Foley catheter, Medtronic Electronics Inc. Parker, CO, USA) was used. An arterial catheter was placed in the radial or femoral artery for continuous invasive blood pressure monitoring and blood sampling. ECG, peripheral oxygen saturation, end-tidal CO_2, and respiratory rate as standardized intensive care monitoring was established. Relaxation depth was measured using the TOF watch® SX (Organon Teknika B.V., Boxtel, Netherlands) in intervals of three hours during the cooling period, and in 30 min intervals after 29 h – at the time of termination of continuous study medication therapy – while rewarming

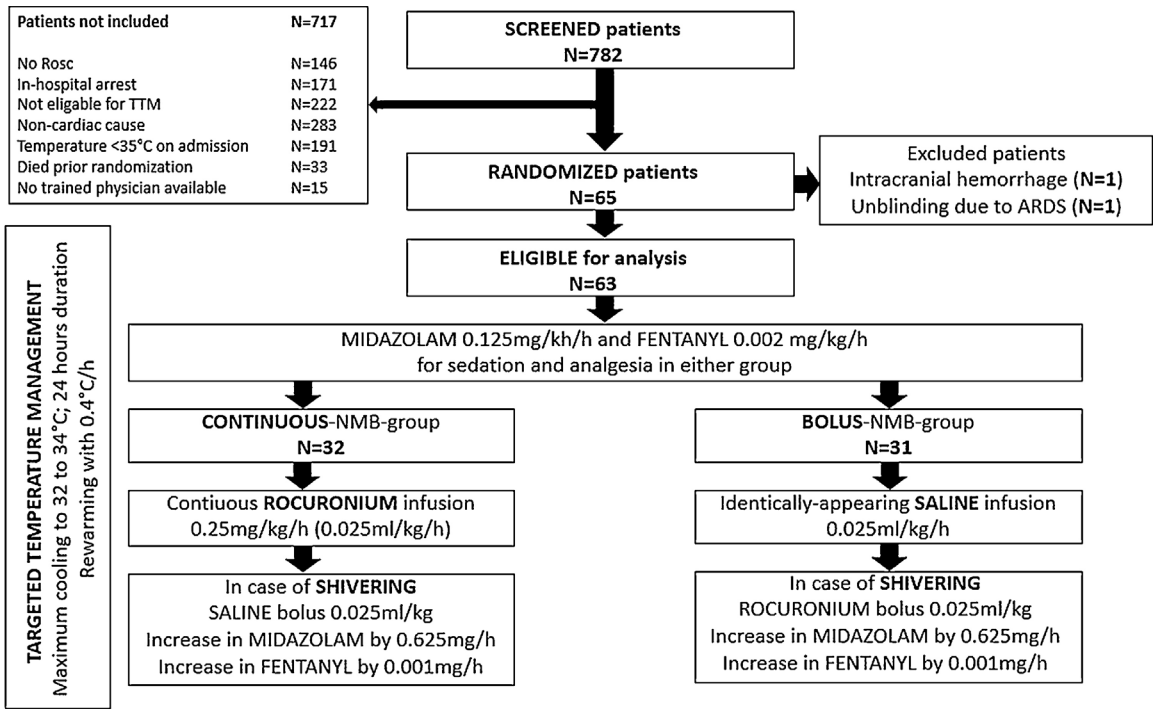

Fig. 1. Flowchart of study procedures. OHCA: out of hospital cardiac arrest. ARDS: acute respiratory distress syndrome.

to 36° C body core temperature. TOF-measurements were done by a person who was not involved in the clinical management of the patients and results had no influence on the administered dosage of rocuronium to ensure a blinded relaxation management.

Neurologic function was assessed at 1, 2, 6 and 12 month during the follow up period and contained Glasgow Coma Scale (GCS), Pittsburgh Brain Stem Score (PBSS), Cerebral Performance Category score (CPC), and Overall Performance Category score (OPC).

A performance score of 1 (good function) or 2 (moderate disability) on a 5-category CPC scale was considered as a good neurologic recovery; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death). Cooling effort was determined by manually calculating the cooling rate from start of cooling until reaching the target temperature. As an estimate of the cooling device activity and effort during the maintenance phase of TTM the theoretical heat transfer between the given patients' body temperature and the temperature of the devices cool bath was used. The following formula was used: Q/min (J/min) = [C_{NaCl} * Flow * (T_{bath}-T_{pat})]/1000; (C_{NaCl} = heat capacity of saline; Flow = flow of saline through catheter; T_{bath} = water bath temperature; T_{pat} = patient temperature) [16].

Incidence of critical illness polyneuropathy and myopathy was evaluated by an independent neurologist 12 months after cardiac arrest by means of clinical examination and nerve conduction studies.

Statistical analysis

At a two-sided type-I error level of 5% and with a power of 80% we calculated a necessary sample size of 26 participants per group with an 1:1 allocation ratio to detect a significant difference of 32% probability of at least one shivering episode. We increased this formal sample size to allow for potential missing data such as for early mortality.

We present categorized variables as absolute counts and relative frequencies, and continuous variables as mean and standard deviation or median and 25–75% quartiles as appropriate. We tabulated baseline and demographic variables according to study group allocation. We do not present formal hypothesis test results for assessing randomization success.

We compared the number of study medication boluses between the study groups using the Mann Whitney *U* test. After categorizing this outcome as 0, 1–3, 4–10, 10+, we used a chi-squared test for formal hypothesis testing. For the secondary outcomes we used the same hypothesis testing strategies, according to data distribution. Neurological outcome was assessed as a binary variable, where we additionally calculated a relative risk with an exact 95% confidence interval. We used survival analysis to assess the effect of study group allocation on mortality with study start as entry, exit as the end of follow up and death from all causes as failure. We used a proportional hazards Cox model to estimate a hazard ratio with a 95% confidence interval.

For data management and analyses, we used MS Excel for Mac (Microsoft Inc., Redmond, WA, USA) and Stata 11 for Mac (StataCorp LLC, College Station, TX, USA). Generally, a two-sided *p*-value less 0.05 was considered statistically significant.

Results

From November 2010 to September 2013 sixty-three patients (32 continuous-NMB-group; 31 bolus-NMB-group) were enrolled (Fig. 1). Mean age was 60 ± 12 years and the majority were male (83%). In the majority of included patients the first monitored ECG showed a shockable rhythm (86%). Differences in baseline characteristics at hospital admission were not significant (Table 1).

Primary outcome

Shivering episodes were detected in 29/31 patients (94%) in the bolus-NMB-group compared to 8/32 patients (25%) receiving continuous rocuronium infusion with a median of 0 shivering episodes in the continuous-NMB-group (interquartile range [IQR] 0–0.5 episodes) and 8 episodes (IQR 4–12 episodes) in the bolus-

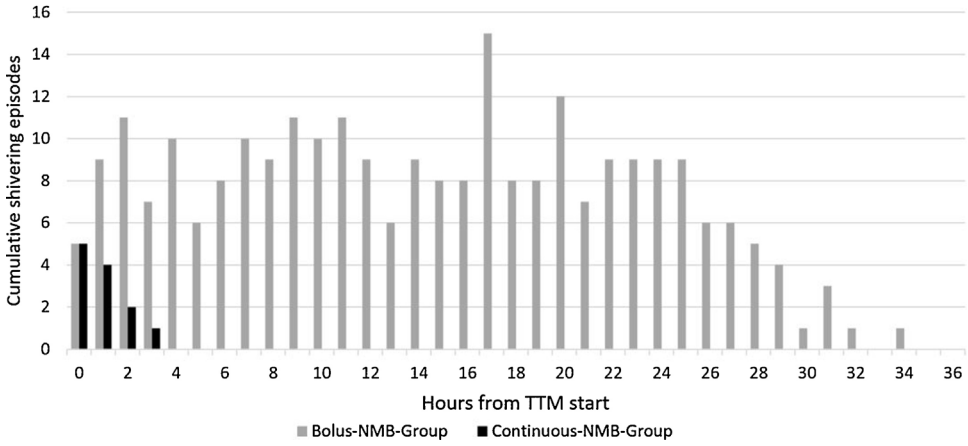

Fig. 2. Cumulative shivering episodes during targeted temperature management.
Cumulative shivering episodes in a resolution of one hour showing shivering episodes in the continuous-NBM-group only in the first three hours. In the bolus-NBM-group shivering was observed throughout the TTM treatment.

Table 1
Baseline characteristics.

	Continuous-NMB-group	Bolus-NMB-group
	N = 32	N = 31
Age, years – mean (SD)	62 (13)	58 (11)
Male gender – n (%)	26 (81)	26 (84)
BMI, kg/m^2 – mean (SD)	28 (6)	28 (4)
Witnessed CA – n (%)	29 (91)	28 (90)
No BLS – n (%)	12 (38)	11 (35)
No flow, min – median (IQR)	2 (1;5)	1 (1;3)
Low Flow, min – median (IQR)	18 (11;24)	16 (12;29)
Initial rhythm VF – n (%)	26 (81)	28 (90)
Admission, min after ROSC – median (IQR)	34 (31;50)	34 (18;55)
Prehospital administration of NMB – n (%)	14 (44)	20 (63)
pH on admission – mean (SD)	7.18 (0.11)	7.16 (0.13)
Lactate on admission, mmol/l – mean (SD)	7.3 (3.6)	6.9 (3.5)
Glucose on admission, mg/dl – mean (SD)	256 (90)	252 (85)
GCS on admission – median (IQR)	3 (3;5)	3 (3;3)
PBSS on admission – median (IQR)	8 (6;9)	9 (7;10)
Core temperature on admission, °C – mean (SD)	35.9 (0.6)	35.8 (1.0)

Abbreviations: SD, standard deviation; BMI, body mass index; CA, cardiac arrest; BLS, basic life support; IQR, interquartile range, VF, ventricular fibrillation; ROSC, return of spontaneous circulation; NMB, neuromuscular blockade; GCS, Glasgow coma scale; PBSS, Pittsburgh Brain Stem Scale.

NMB-group ($p < 0.01$). Shivering episodes in the bolus-NMB-group occurred throughout the TTM period (Fig. 2).

Secondary outcomes

Patients randomized to the continuous-NMB-group received significant lower doses of midazolam (4.3 ± 0.8 mg/kg vs. 5.1 ± 0.9 mg/kg, $p < 0.01$) and fentanyl (0.062 ± 0.014 mg/kg vs. 0.071 ± 0.007 mg/kg, $p < 0.01$), but required higher cumulative doses of rocuronium (7.8 ± 1.8 mg/kg vs. 2.3 ± 1.6 mg/kg, $p < 0.01$). TOF-Watch measurements in the continuous-NMB-group showed deep relaxation until the end of rocuronium administration whereas the median relaxation depth was less in the bolus-NMB-group (Fig. 3). Patients in the continuous-NMB-group woke up earlier (2 [IQR 2;3] days vs. 4 [IQR 2;7.5] days, $p = 0.04$) and had a shorter length of stay at the ICU (6 [IQR 3;5.9] days vs. 10 [IQR 5;15] days, $p = 0.03$). There was no significant difference in overall mortality (continuous-NMB-group 15/32 [47%] vs. bolus-NMB-group 12/31 [39%], hazard ratio 1.34 [95% CI 0.63-2.87], $p = 0.45$) nor in the rate of favourable neurologic function after 12 months of observation (continuous-NMB-group 17/32 [53%] vs. bolus-NMB-group 17/31 [55%], risk ratio 0.97 [95% CI 0.61-1.53], $p = 0.89$). (Table 2) Continuous administration of NMBs neither influenced the cooling rate (continuous group mean 3.3 ± 1.4 °C/h versus bolus group mean 3.2 ± 1.5 °C/kg/h, respectively; $p = 0.81$) nor the time to achieve target temperature (continuous-NMB-group: mean 45 min [IQR 23;58] vs. bolus-NMB-group: 31 min [IQR 13;75] $p = 0.36$).

Table 2
Causes of mortality.

	Continuous-NMB-group	Bolus-NMB-group	p-value
	N = 32	N = 31	
Overall mortality – n (%)	15 (47)	12 (39)	0.45
Time to death – days (IQR)	9 (3;22)	15 (7;40)	0.37
Causes of death			
Neurologic – n (%)	8 (53)	7 (59)	0.80
Cardiac – n (%)	7 (47)	4 (33)	0.48
Sepsis – n (%)	0 (0)	1 (8)	0.26

Abbreviations: IQR, interquartile range.

Patients receiving a continuous NMB therapy had a significantly lower heat transfer rate compared to the bolus-NMB-group (−3602 J/min [IQR −5527;−1724]) vs. (−6776 J/min [IQR −9421;−4368]) ($p < 0.01$).

Neurological examinations at one year (clinical examination and nerve conduction) were available only in six patients of the continuous-NMB-group and in three patients in the bolus-NMB-group. Signs of polyneuropathy were found in two patients of the bolus-NMB-group and in two patients of the continuous-NMB-group.

Discussion

In this randomized, controlled trial, in patients successfully resuscitated from OHCA and received TTM at levels of 32 °C–34 °C a continuous neuromuscular blockade during the therapeutic course of TTM leads to a significant reduction in shivering episodes compared to a demand-orientated bolus administration. Furthermore, continuous NMB administration contributes to a reduced dosage

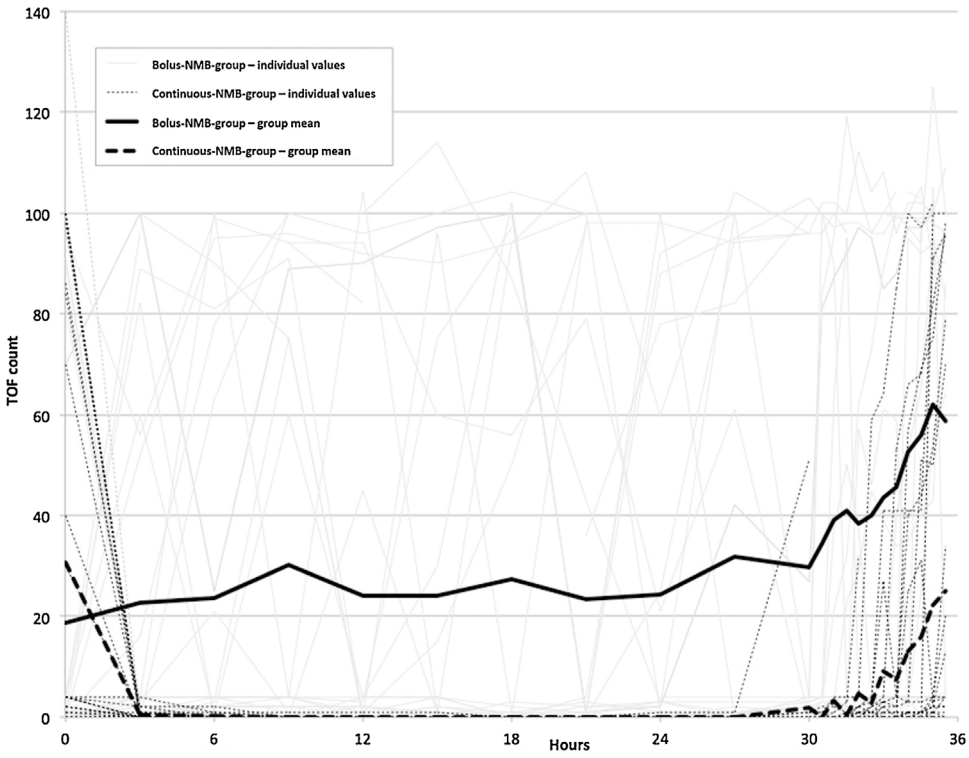

Fig. 3. Train of four (TOF) counts during targeted temperature management.
Measurements were done every 180 min during induction and maintenance phase. After 29 h measurements were executed every 30 min during rewarming. TOF-count is calculated as the response to 4 identical electrical stimuli. The relation between the first response and the last response is expressed in percentage. If less than four responses were detected (up to no answer out of four stimuli) the TOF count is expresses in this diagram as 0%.

of sedative/analgesic drug use. Therefore, early awakening and a reduced length of stay in the intensive care unit was observed.

Up to now, the optimal treatment to reduce shivering in patients undergoing TTM is still a matter of debate. It is widely accepted, that shivering should be avoided, because it could lead to temperature counter-regulation, to an increase in metabolic demands, a reduction in cooling rate and thereby could counteract the beneficial effects of TTM [6].

Although we did not demonstrate a reduction in cooling rate, an increased cooling effort was necessary in the bolus-NMB-group. This leads to the assumption of an increased heat production caused by a higher metabolic rate in this patient. Despite a stepwise protocol of NMB therapy for shivering prevention Lascarrou et al. described the necessity of a continuous administration as final level of escalation in most patients [17]. This corresponds to our study, in which all patients in the bolus-NMB-group had multiple episodes of shivering and received multiple applications together with an increase in sedative/analgesic therapy. Otherwise shivering was only seen in one third of the patients in the TTM-Trial. But detailed information about the NMB administration are lacking [18]. An interrater variability of the 'Shivering Assessment Scale' used in this trial could explain different shivering rates in the literature. Patients in the continuous-NMB-group received a 3-fold higher dose of rocuronium than patients in the bolus-NMB-group. In contrast, they received a significant lower dose of midazolam and fentanyl. This is at least in part a result of our treatment protocol, where the continuous sedative/analgesic therapy had to be increased if shivering was noticed. Still we observed no clinical signs of undersedation in the bolus-NMB-group nor in the continuous-NMB-group. As a result, time to awakening as well as duration of intensive care unit stay was shorter in patients in the continuous-NMB-group.

As shivering was observed during the whole period of TTM in the bolus-NMB-group our results are in contrast to the current opinion, that shivering would be a problem of specific time-frames during the treatment course of TTM (i.e. the induction phase and the rewarming phase) [12].

NMB have shown to decrease inflammatory response and increase the probability of survival in patients with acute respiratory distress syndrome [9,19]. As ischemia/reperfusion injury after cardiac arrest is associated with a diffuse inflammation process the use of NMBs might directly influence outcome [8,9,20,21]. No significant benefit in either neurologic function or overall survival due to continuous NMB administration was evident in our study. Especially, the higher metabolic rate in the bolus group might counteract the beneficial effect of TTM [22]. As this was not the primary outcome of our study it might have been underpowered to detect a difference.

Neuromuscular blocker agents are associated with the occurrence of polyneuropathy and myopathy during and after the further intensive care stay. Studies evaluating risk factors for a critical illness polyneuropathy and myopathy show divergent results [23]. According to a recently published study [10], the monitored use of NMB, whether continuous (<48 h) or bolus administration, should be considered safe and efficacious. Due to the lack of neurological assessments at one year in most survivors our study is insufficient to adequately answer this question.

Our study has some further limitations. First of all, our primary outcome parameter is as surrogate parameter which might or might not be associated with an overall benefit for OHCA patients. Furthermore, the role of NMB administration might be altered in combination with another sedative/analgesic regimen. Although the shown reduction in cumulative dose of sedative/analgesic therapy would be also expected in combination with other therapies and might lead to earlier neurologic prognostication and shorter

ICU stay. Not at least the use of NMBs may mask seizure activity, which might be undetected in our study. However, the dosage of midazolam should have been appropriate to suppress seizure activity and therefore this might be negligible but the use of a continuous EEG-monitoring might be reasonable. The study population consisted of mostly witnessed cardiac arrest cases with predominant shockable rhythm arrests. Therefore our results may not be generalizable to the broader post arrest population.

Conclusion

In patients after OHCA treated with TTM continuous as compared to bolus neuromuscular blockade administration reduced shivering, time until awakening, and duration of intensive care unit stay without significant harm.

Conflict of interest statement

None.

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