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Effect of Administration of Neuromuscular Blocking Agents in Children with Severe Traumatic Brain Injury on Acute Complication Rates and Outcomes: A Secondary Analysis from a Randomized, Controlled Trial of Therapeutic Hypothermia

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Abstract

Objective—To evaluate the association between neuromuscular blocking agents (NMBA) and outcome, intracranial pressure (ICP) and medical complications in children with severe TBI.

Design—A secondary analysis of a randomized, controlled trial of therapeutic hypothermia.

Setting—17 hospitals in US, Australia, and New Zealand

Patients—Children (< 18 y) with severe TBI.

Interventions—None for this secondary analysis.

Measurements and Main Results—Children received NMBA on the majority of days of the study (69.6%) and the modified Pediatric Intensity Level of Therapy (mPILOT) scores (modified by removing NMBA administration from the score) were increased on days when NMBA were used (9.67 ± 0.21 vs. 5.48 ± 0.26 , $p < 0.001$). Children were stratified into groups based on exposure to NMBA (Group 1 received NMBA each study day; Group 2 did not). Group 1 had increased number of daily ICP readings > 20 mmHg (4.4 ± 1.1 v. 2.4 ± 0.5 , $p = 0.015$) and longer ICU length of stay (LOS) and hospital length of stay ($p = 0.003$ and 0.07 , respectively, Kaplan-Meier). The Glasgow Outcome Score – Extended for Pediatrics at hospital discharge, 3 mo, 6 mo

and 12 mo after TBI and medical complications observed during the acute hospitalization were similar between groups.

Conclusions—Administration of NMBA was ubiquitous and daily administration of NMBA was associated with intracranial hypertension but not outcomes – likely indicating that increased injury severity prompted their use. Despite this, NMBA use was not associated with complications. A different study design – perhaps using randomization or methodologies – of a larger cohort will be required to determine if NMBA use is helpful after severe TBI in children.

Keywords

traumatic brain injury; guidelines; neuromuscular blockade; pediatric neurocritical care; intracranial hypertension

Introduction

Unintentional injury is the leading cause of death in the United States among 1–18 year olds, and traumatic brain injury (TBI) was the cause of almost 50% of these deaths – accounting for over \$50 billion in costs (1, 2). In the management of severe TBI in children, sustained intracranial hypertension - and potential cerebral hypoperfusion - has long been recognized as an insult to be avoided and treated (3, 4). In 2003, the Brain Trauma Foundation (BTF) Guidelines panel recommended a clinical pathway that identified various tiers of therapies for the prevention and treatment of intracranial hypertension (5), with first tier therapies including elevation of the head of the bed, drainage of cerebrospinal fluid, hyperosmolar therapy with hypertonic saline or mannitol, and administration of sedatives in conjunction with neuromuscular blocking agents (NMBA) among the recommendations. Subsequently in 2012, the published guidelines were updated, yet this document emphasized the requirement for additional data to better inform many aspects of TBI care (6). Of the 15 therapeutic areas discussed in the updated version of these guidelines that were published in 2012, no topic had sufficient evidence to generate a Class I treatment recommendation – such a recommendation would signify that the treatment “must be done”. Moreover, only 4 topics have sufficient evidence to support a Level II treatment recommendation, signifying that the treatment “should be considered”. The remaining recommendations are Class III - indicating that these therapies that make up the bulk of the recommendations “may be considered” for children with severe TBI.

One of the least studied areas is the use of NMBA to improve cerebrohemodynamics and ultimately neurological recovery, for which no recommendations could be generated by the guidelines committee (6, 7). It has been postulated that as NMBA decrease intrathoracic pressure as a result of the decreased muscular tone, then cerebral venous return could be improved that results in decreased intracranial pressure (ICP) (8, 9). However, this theory remains speculative as a study of 24 severely brain injured adults found that a single bolus dose of cisatracurium did not have a measurable effect on ICP (10). In children, NMBA have been shown to significantly reduce overall body metabolism and oxygen consumption, which may indirectly have beneficial effects for children with severe TBI (11). Overall, the risk/benefit profile of NMBA in children with severe TBI and other conditions is generally understudied – with the benefits of improved synchrony with mechanical ventilation,

reduced shivering and decreased muscular activity during period of agitation being weighed against potential risks of increased risk of infections (including pneumonia, central line-associated blood stream infections [CLABSI] and others), masking of the neurological examination (and possible seizures), possible increased risks of thromboembolism due to immobilization and potential hypoxemia/hypercarbia which can result from unintended extubation or mechanical obstruction of the airway (12–14).

Because there has not been a systematic examination of the association between NMBA and important outcome parameters in children with severe TBI (either overall outcome or surrogates such as ICP-directed therapies), we interrogated a database that was generated from a phase III study of early, therapeutic hypothermia (Pediatric Traumatic Brain Injury Consortium: Hypothermia or the “Cool Kids Trial”) (15). We hypothesized that increased exposure to NMBA in pediatric TBI patients would be associated with improvements in intracranial hypertension and neurological outcome, and that NMBA would not be associated with increased complications.

Methods

Informed consent was obtained from all participants in this study. Specifically, principal investigators at each participating institution obtained informed consent from parents/guardians for randomization to receive hypothermia or normothermia treatment. In one center, emergency waiver of consent for randomization followed by obtaining consent from the parents was permitted and one subject was enrolled in this manner. As a part of the overall study, details regarding a number of medical treatments, including the administration of medications such as NMBA, were collected as part of routine data collection for the study. This is a secondary analysis of these data.

The Cool Kids Trial was a phase 3, multi-national, randomized, controlled trial designed to assess the efficacy of early, moderate hypothermia (32–33°C) with slow rewarming on mortality after pediatric traumatic brain injury, as recently reported (15). Specifically, children were randomized to receive hypothermia for 48 hours or controlled normothermia – with randomization required within the first 6 hours after injury. Children were eligible for inclusion if they were less than 18 years of age, had a Glasgow coma scale (GCS) ≥ 8 , a GCS motor score < 6 after resuscitation and were available to be randomized within 6 hours after injury. Exclusion criteria included a normal head CT, Glasgow coma score of 3 with unreactive pupils, hypotension for > 10 minutes (defined as $< 5^{\text{th}}$ percentile for age), uncorrectable coagulopathy, hypoxia (oxygen saturation $< 90\%$ for > 30 min after resuscitation), pregnancy, penetrating injury and unavailability of a parent or guardian to consent at centers without emergency waiver of consent. Randomization and masking procedures have been previously described and children were enrolled at a total of 17 study hospitals in the USA, New Zealand, and Australia.

A clinical protocol was suggested for all study sites participating in the trial, including treatment of intracranial hypertension and other clinical parameters. Specifically, study sites were given specific instructions on cooling and rewarming the subjects that were required to be followed. As a part of this instruction, sites were urged to maintain neuromuscular

blockade during the cooling period and during rewarming to prevent shivering. However, sites were able to utilize these medications as well as other aspects of care (when to start nutrition, when to start glucose, use of insulin, treatment of side effects including pneumonia/sepsis and others) at their own discretion. In addition, all sites were free to use their clinical standards of care regarding NMB monitoring – including the performance of train-of-four testing, the use of drug holidays and other techniques to mitigate the side effects of NMBA use. An intracranial hypertension algorithm consistent with evidenced-based guidelines was provided to the sites and compliance with this algorithm was strongly encouraged.

Data collection for the study was extensive during the first 7 days of hospitalization. Specifically, hourly (physiologic data [including ICP, mean arterial pressure (MAP), cerebral perfusion pressure (CPP = MAP – ICP), temperature (rectal, brain and others)]) and daily (fluid volumes, specific medications that were administered, pediatric intensive level of therapy [PILOT] scores (16) and laboratory data) data was recorded to monitor the safety and reliability of the trial. As a part of the routine conduct of the clinical trial, pre-defined Adverse and Serious Adverse Events (AEs and SAEs) were compiled by site personnel and reviewed by an independent safety monitor to ensure the safety of the therapeutic trial. For this secondary analysis, we selected a subset of these complications to determine the association between NMBA exposure and these events (see Table 1). For medications administered, including NMBA, the administration of the medication at any point during the day within the study period was recorded by site study coordinators. However, data describing neuromuscular monitoring techniques (outlined above) were not recorded within the study database and therefore, were not available for analysis.

For this secondary analysis, we made several modifications of the routinely collected data of the overall study. Since our hypothesis for the association between NMBA use and outcomes was specific for at least some long-term use of NMBA (hours to days), we excluded succinylcholine exposure from this analysis. Due to its short half-life (< 5 minutes), we chose not to determine the effect of this medication on overall TBI outcomes for our analysis. Therefore, exposure to the medications rocuronium, vecuronium, pancuronium and cis-atracurium were included within this analysis and are referred to as “NMBA exposure” from this point forward in the manuscript. Moreover, since the PILOT scores include the use of NMBA as an intrinsic part of the scoring system, we developed a modified version of the PILOT score (mPILOT), which excludes the use of NMBA in generating the score within this secondary analysis to eliminate bias. Primary outcomes for the overall study and for this analysis were the Glasgow Outcome Score Extended for Pediatrics score (GOS-E Peds) - a validated measure of overall outcome after TBI - at hospital discharge and at 3, 6, and 12 months after hospital discharge (17). The sample size required to detect a 2 point difference on the GOS-E Peds score assuming a maximum acceptable type 1 error rate of 0.05 and a type 2 error rate of 0.2 is 22 patients per group. Additional analyses for this study utilized secondary outcomes including ICU length of stay, hospital length of stay, number of daily ICP readings > 20 mm Hg, number of CPP readings < 50 mm Hg, and the incidence of a priori-defined complications of TBI (described above).

In a preliminary analysis, we compared the mPILOT scores on all days of NMBA exposure to all days without NMBA exposure of all subjects. Subsequently, children were stratified based on exposure to NMBA into 2 groups – Group 1 was exposed to NMBA each day during the study period and Group 2 did not receive NMBA on each day of the study period (either intermittent or no exposure at all to NMBA). For subjects who died within the first 7 days of hospitalization, they were included in Group 1 if they received NMBA on each day they were enrolled in the study. Groups were compared using the Mann-Whitney U test for continuous and ordinal variables and the Pearson χ^2 statistic with Yates' continuity correction or Fisher's exact test for nominal variables. Intergroup differences in ICU length of stay and hospital length of stay were compared using a Kaplan-Meier survival analysis using a log-rank test. We used generalized estimating equations with an independent correlation structure to examine the effect of covariates on the GOS-E Peds and mPILOT score. Statistical analysis was performed using SPSS Statistics version 20 and SAS version 9.2. Statistical significance is defined as $p < 0.05$. Data are presented as mean $\pm$ standard error of the mean (SEM), unless otherwise noted.

Results

Ninety children were available for analysis, including 77 children who were randomized to hypothermia or normothermia and 13 run-in subjects (whom all received hypothermia). Thirty-one children met criteria for Group 1, and 59 children met criteria for Group 2. Out of the 59 children in Group 2, 55 children received NMBA at some point [range 1 – 6 d]. The distribution of the randomization to therapeutic hypothermia is as follows: TH: 52 children overall, 17 children in Group 1, 35 in Group 2; Normothermia: 38 children overall, 14 children in Group 1 and 24 in Group 2. Of all children receiving NMBA during the data collection period ($n = 86$), 97% of these subjects received vecuronium, 58% received rocuronium, and 3% received pancuronium. Of the 86 children receiving NMBA during the data collection period, 57% received two or more NMBA. Baseline characteristics were similar between groups 1 and 2 (see Table 2), including the proportion of receiving therapeutic hypothermia (55% in group 1, 59% in group 2). Sixty-three percent (63%) of children were boys, 74% of children were white, 17% were black, and 9% were of another racial origin. Twenty-one percent (21%) of children reported Hispanic ethnicity. Overall, the mean age was 114 months, the median GCS score was 6 (5–7, IQR). Three out of the 17 participating sites enrolled 53% of the children: Children's Hospital of Pittsburgh, PA, USA (24 children), University of California, Davis, CA, USA (13 children), and University of Texas, Southwestern, TX, USA (11 children).

Out of 602 patient-days of observation, subjects received NMBA on 419 days (69.6% of days). On the days that patients received at least one dose of a NMBA, mPILOT scores were increased compared to days when no NMBA was administered (9.7 ± 0.2 v. 5.5 ± 0.3 , $p < 0.001$). GOS-E Peds scores at hospital discharge and at time points after discharge were not different between Group 1 and Group 2 (hospital discharge: 6.3 ± 0.2 v. 6.1 ± 0.2 , $p = 0.57$; 3 mo: 4.4 ± 0.5 v. 4.3 ± 0.3 , $p = 0.91$; 6 mo: 4.7 ± 0.5 v. 4.3 ± 0.3 , $p = 0.33$; 12 mo: 4.2 ± 0.5 v. 4.0 ± 0.3 , $p = 0.49$; Figure 1). GOS-E Peds scores at hospital discharge and at time points after discharge were not different between children that received a single NMBA compared to those who received two or more NMBAs.

Based on the Kaplan-Meier analysis, there was a significant group effect for both time to ICU discharge and time to hospital discharge with group 2 having a shorter duration of both measures ($p = 0.003$ and $p = 0.07$, respectively, Figure 2). Group 1 had an increased frequency of ICP readings > 20 mmHg (4.4 ± 1.1 vs. 2.4 ± 0.5 readings/day, $p = 0.015$) but no difference in frequency CPP readings < 50 mmHg (3.0 ± 1.0 vs. 1.7 ± 0.4 readings/day, $p = 0.238$). Rates of medical complications including death, pneumonia, wound infection, positive cultures from catheters, other infections, hypotension, and seizures were similar between group 1 and group 2 (Table 3). Rates of the same medical complications mentioned above were similar between children who received a single NMBA and those who received 2 or more NMBA.

Covariates selected for the regression model were randomization assignment to hypothermia or normothermia, gender, age, and Glasgow coma score after initial resuscitation. Of these covariates, only the Glasgow coma score at the time of admission was significantly associated with a change in the GOS-E Peds score (1 point increase in GCS associated with a 0.4 point improvement in GOS-E Peds, $p < 0.001$). Randomization assignment to hypothermia versus normothermia, gender, and age were not correlated to a change in the GOS-E Peds score. None of the selected covariates were correlated to a change in the mPILOT score.

Discussion

In this cohort of children within a RCT for therapeutic hypothermia for severe TBI, use of NMBA was quite ubiquitous, with nearly all children receiving agents in the days immediately following the injury and NMBA administration noted on almost 70% of all hospital days for the entire cohort. We found that NMBA use was associated with an increase in ICP-related therapies on these days for the entire cohort. Because of the use pattern of NMBA in the cohort, we stratified patients into children who had received NMBA each day of the first week and compared this group to children who had received NMBA on a more intermittent basis during this time period – and we found that there was no difference in overall outcome based on this factor. Consistent administration of NMBA was associated with intracranial hypertension and increased ICU LOS. However, it was not associated with an increase number of medical complications.

Overall, this is the first analysis of NMBA usage in children with severe TBI in the literature to our knowledge. The topic of NMBA use in adults after severe TBI was addressed by Hsiang and colleagues from data derived from the Traumatic Coma Data Bank (TCDB) decades ago (18). In their analysis of subjects injured between the years 1984 – 87, the authors analyzed 514 subjects and stratified subjects into two groups – those who received NMBA early after injury and those who did not – with 46.5% of subjects stratified into the NMBA group. It is difficult to compare this finding with our data, as we found 95.6% of subjects received NMBA overall and 34.4% received NMBA every day for the first 7 days. However, it seems likely that NMBA usage in our cohort was more widespread than the TCDB subjects – possibly because of differences in care for children vs. adults, the need for concomitant use of NMBA to facilitate hypothermia treatment or other factors. In this adult cohort, the authors found an increase ICU LOS, an increased incidence of pneumonia, but

also a survival benefit (24% vs. 39%, $p < 0.001$) with NMBA use. They did not, however, find a difference in overall favorable outcome of the groups because the use of NMBA was associated with an increased incidence of severely disabled and vegetative subjects. In contrast, we did not observe a mortality/outcome effect or an increased incidence of any of a number of complications including pneumonia with NMBA usage based on the definitions used within our study. However, we also found that NMBA usage was associated with prolonged ICU LOS.

In critically-ill subjects and those with general trauma, more data are available regarding NMBA use and complications. Perhaps the strongest concern regarding NMBA use is the risk of critical illness polyneuropathy with concomitant use of NMBA with steroids in patients with sepsis (8). Other studies have demonstrated increased pneumonia and infection rates in children and adults treated with NMBA, likely due to diminished ability to clear respiratory secretions effectively during immobilization. In a comprehensive study of almost 1000 admissions to a pediatric ICU, Fayon and colleagues found that NMBA use was associated with bacterial pneumonia after controlling for more than a dozen potential covariates (12). Moreover, Hanson and colleagues demonstrated that NMBA use in children with trauma is associated with a 10-fold increase in venous thromboembolism (13). Despite these concerns, a recent double-blinded, randomized controlled trial of NMBA use in adults with severe lung disease demonstrated that subjects randomized to cisatracurium had > 9% overall decrease in 28-day mortality (23.7% vs. 33.3%, $p = 0.05$) (19). In our study, we did not observe beneficial or detrimental effects of NMBA on such outcomes, likely because the sample size was not sufficient to generate sufficient statistical power. To answer these questions, it seems likely that a larger cohort study or a different study design will be required.

In pediatric TBI, the use of NMBA was included as a first-tier therapy for intracranial hypertension control in evidence-based guidelines since 2003 (5). In these guidelines, while recommending that their use be left to the treating clinician based on the lack of sufficient evidence, the experts on the panel recommended the use of NMBA within the algorithm as a “first-line” therapy based on their experience. The paucity of evidence for the indications for use of NMBA is reflected more broadly in the UK Paediatric Intensive Care Guidelines from 2007, which simply recommend a case-by-case evaluation of the risks and benefits of NMBA in children with critical illness (20). In the more recent guidelines from 2012, no new studies were identified to answer this important question (6). In our study, we attempted to define whether or not the use of NMBA was associated with alterations in the burden of ICP in two ways. First, we found that consistent exposure to NMBA in our cohort was associated with an increased number of hours of intracranial hypertension – a finding that Hsiang and colleagues failed to find in their analysis of adult subjects from the TCDB (18). Second, we used a modification of the PILOT score in two ways – analyzing days of NMBA use amongst the entire cohort and also in our patient stratification. Theoretically, it is possible that NMBA could have a number of salutary effects on cerebrohemodynamics after TBI. Vernon and colleagues demonstrated that administration of NMBA in children resulted in significant decreases in energy expenditure and oxygen consumption – both of which might be beneficial to mitigate against constraints of cerebral blood flow to meet metabolic demands at times when this might be critical after TBI (11). Unfortunately, it is not possible

using our study design to determine if NMBA are an effective treatment of intracranial hypertension. Our data suggests that more consistent NMBA use is associated with increased ICP, but this could be an epiphenomenon.

In addition to those outlined above, our analysis has a number of limitations. First, our data collection system for the Cool Kids Trial only documented if NMBA were administered on each day after TBI, and the total exposure to NMBA (including dose of each administration, number of administrations and cumulative exposure to NMBA) could not be determined using the existing system within the trial. During the development of the clinical trial, the study team considered collecting detailed information on medication administration for drugs such as NMBA. However, it became clear that such an intense data collection system that would be required to collect this information on NMBA or other individual drugs of interest (sedatives, pentobarbital, vasopressor medications) was a burden on the clinical sites that made the overall trial unfeasible. Moreover, there was no documentation of hepatic or renal impairment for study subjects, factors that could strongly influence the pharmacokinetics of NMBA, leading to stronger pharmacodynamics effects not accounted for by data on NMBA dosing. Therefore, for this analysis, we were limited in our determination of exposure to NMBAs. Second, while the Cool Kids Trial was performed at more than 30 clinical sites, three sites outlined above contributed a substantial plurality of patients into the study (University of Pittsburgh, University of California/Davis and University of Texas-Southwestern). Given the relatively small sample size, it is likely that these three institutions influenced the data within the clinical trial, which could limit generalizability. Lastly, the data for this study were collected as part of a randomized trial of therapeutic hypothermia – and this may have profound effects on clinician choices of medications and the medication's effects. The clinical protocol recommended that shivering be avoided and required the use of NMBA during cooling and rewarming. However, clinical sites were free to care for children as they felt appropriate, including whether to administer NMBA and how to monitor their effectiveness. Recent evidence suggests strongly that therapeutic hypothermia can have profound effects on drug disposition and actions (21, 22) – emphasizing the need for further study of this important topic.

In conclusion, this is the largest study in children with severe TBI to describe the impact of NMBA use – a therapy that is recommended as a Tier 1 therapy despite little clinical evidence. We found that NMBA use – as defined within our dataset that was intended to study the effect of hypothermia – was not associated with an increased number of complications, and it was used in patients who had increased intracranial hypertension. Overall, a different study design – that includes randomization of children into groups to undergo neuromuscular blockade or a larger, cohort study outside the context of a hypothermia trial – will be necessary to fully answer the questions regarding the utility of NMBA use for children after severe TBI.

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Figure 1.

Glasgow Outcome Score Extended for Pediatrics (GOS E-Peds) for children in the Cool Kids trial at hospital discharge, 3 mo, 6 mo and 12 mo after injury stratified based on the exposure to NMBA. Group 1 (hatched-bars) received NMBA each of the first 7 days of the study while Group 2 (open bars) was not exposed to NMBA on each day of the study. GOS-E Peds scores were similar between group 1 and group 2 at all times (hospital discharge: 6.3 ± 0.2 v. 6.1 ± 0.2 , $p = 0.57$; 3 mo: 4.4 ± 0.5 v. 4.3 ± 0.3 , $p = 0.91$; 6 mo: 4.7 ± 0.5 v. 4.3 ± 0.3 , $p = 0.33$; 12 mo: 4.2 ± 0.5 v. 4.0 ± 0.3 , $p = 0.49$).

Figure 2.

Kaplan-Meier survival analysis comparing the percentage of group 1 (solid line) and group 2 (dashed line) remaining (A) in intensive care unit (ICU) and (B) in the hospital. There was a significant group effect for both time to ICU discharge and time to hospital discharge with group 2 having a shorter duration of both measures ($p = 0.003$ and $p = 0.07$, respectively).

Table 1

Definitions of complications of traumatic brain injury

Complication	Definition
Death	Death of a subject from any cause within the follow-up period of the study (12 months)
Pneumonia	Three pieces of data are required for the diagnosis including radiographic, clinical evidence and clinical signs Radiographic evidence: On 2 or more serial chest radiographs of at least 1 of the following: (i) a new or progressive infiltrate, (ii) persistent infiltrate, (iii) consolidation, (iv) cavitation or pneumatocele Clinical evidence: At least 1 of the following: (i) fever > 38.5°C, abnormal WBC (< 4,000/ml or > 12,000/ml) Clinical signs: At least 2 of the following: (i) new onset purulent sputum, (ii) change in sputum character, (iii) increased respiratory secretions, (iv) increased suctioning requirements, (v) worsening cough/dyspnea, (vi) rales/bronchial breath sounds, (vii) worsening gas exchange (desaturation events, increased oxygen requirements)
Wound infection	Isolation of pathogenic bacteria from a wound (either from the initial trauma or a surgical site) that is treated with antibiotics by the clinical team
Catheter-positive culture	Isolation of pathogenic bacteria from a blood culture from an indwelling catheter with negative blood cultures from other sites, not believed to be contaminated by the processing of the specimen.
Other infections	Recovery of pathogenic organism from a normally sterile site <u>or</u> isolation of a pathogenic organism in a location where it should not be located
Hypotension	Mean arterial blood pressure < 2 standard deviations from age-based norms
Seizures	Observation of a clinically-apparent seizure by an MD <u>or</u> electrographic evidence of seizures as diagnosed by a Pediatric Neurologist

Legend: WBC – white blood cell count

Table 2

Baseline characteristics enrolled in the Cool Kids trial. Data represented as number (percent) or mean $\pm$ standard error of the mean, unless otherwise indicated.

	All (n=90)	Group 1 (n=31)	Group 2 (n=59)
Boys	57 (63%)	17 (55%)	40 (68%)
Ethnic origin			
White	67 (74%)	23 (74%)	44 (75%)
Black	15 (17%)	6 (19%)	9 (15%)
Other	8 (9%)	2 (6%)	6 (10%)
Hispanic	19 (21%)	4 (13%)	15 (25%)
Therapeutic hypothermia	52 (58%)	17 (55%)	35 (59%)
Age (months)	114 $\pm$ 6.9	106.7 $\pm$ 11.9	118.1 $\pm$ 8.4
Weight (kg)	40.9 $\pm$ 2.7	40.3 $\pm$ 5.3	41.3 $\pm$ 3.1
Post-resuscitation GCS (Median [IQR])	6 [5–7]	6 [5–7]	6 [5–7]

Legend: GCS = Glasgow coma score.

Table 3

Number of medical complications in children enrolled in the Cool Kids trial.

	All (n=90)	Group 1 (n=31)	Group 2 (n=59)	p value
Death	12 (13%)	6 (19%)	6 (10%)	0.32
Pneumonia	30 (33%)	8 (26%)	22 (37%)	0.39
Wound infection	1 (1%)	1 (3%)	0 (0%)	0.34
Catheter positive culture	6 (7%)	1 (3%)	5 (8%)	0.66
Other infections	28 (31%)	11 (35%)	17 (29%)	0.68
Hypotension	2 (2%)	1 (3%)	1 (2%)	1.00
Seizures	7 (8%)	2 (6%)	5 (8%)	1.00