Determinants of Pneumonia Risk During Endovascular Hypothermia

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Therapeutic hypothermia is a promising neuroprotective therapy with multiple mechanisms of action. Previously, we demonstrated the feasibility of thrombolysis combined with endovascular hypothermia and an antishivering regimen, but pneumonia occurred more often in cooled patients. We sought to identify whether any factors could be identified that increased pneumonia risk. We examined 26 patients who underwent endovascular hypothermia. Pneumonia was assessed and scored as present by the treating physician without prespecified definitions or surveillance protocols. Using logistic regression, we examined the risk of pneumonia; the effects of age, weight, body mass index (BMI), body surface area, respiration rate, heart rate, blood pressure, baseline National Institutes of Health Stroke Scale (NIHSS), gender, shivering, and area under the curve below 34°C; and total meperidine dose, individually and in a multivariable model. Pneumonia was reported by site investigators in 13 subjects (50%). In univariate analyses, BMI and baseline NIHSS emerged as the baseline variables that were independently associated with risk of pneumonia. Multivariable logistic regression analysis identified baseline NIHSS as marginally associated with risk of pneumonia, after adjustment for BMI (OR: 1.19, 95% CI: 0.98, 1.43; $p=0.0740$). In a group of hypothermia patients suffering a 50% reported incidence of pneumonia, we found no variables that explained risk other than baseline NIHSS. Future trials should include rigorous definitions of pneumonia and prespecified surveillance methods to minimize case ascertainment bias. Measures to prevent pneumonia are needed in all patients treated with hypothermia.

Introduction

THERAPEUTIC HYPOTHERMIA IS PROVEN effective in patients after cardiac arrest and neonatal hypoxia-ischemia, using surface cooling (Bernard, 2002; The Hypothermia After Cardiac Arrest Study, 2002). Such patients are typically sedated, intubated, and chemically paralyzed and so tolerate surface cooling methods. Stroke patients are generally awake and not paralyzed or intubated, which makes it more difficult to overcome homeostatic mechanisms that maintain core body temperature. Endovascular therapeutic hypothermia avoids the problems encountered with surface cooling, notably poor maintenance of target temperature, uncontrolled rewarming, and overshoot to lower temperatures (Krieger, 2001; Schwab, 2001; Abou-Chebl *et al.*, 2004). During endovascular therapeutic hypothermia, intubation is avoided because it increases the incidence of pneumonia (Jumaa, 2010).

In the Intravascular Cooling in the Treatment of Stroke (ICTuS) trial, we combined intravenous meperidine, oral buspirone, and surface warming to control shivering and optimize patient comfort (Mokhtarani, 2001; De Georgia, 2004). In patients who received intravenous thrombolytic therapy in the ICTuS-Longer time window (ICTuS-L) trial, we demonstrated that the combination of hypothermia, antishivering regimen, and thrombolysis did not lead to excessive bleeding complications, but we found an increased incidence of pneumonia in the cooled patients (Hemmen *et al.*, 2010). As there was no increased incidence of sepsis or other infections, we did not suspect a central immune suppression syndrome (Macrez, 2011; Zierath, 2010). Rather, in addition to stroke-related reduction of the immune response, we hypothesized that the risk factors for increased pneumonia incidence are multifactorial. We sought, therefore, to determine the role of several factors using the data from the ICTuS-L trial to

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identify the critical variables that might associate with increased risk of pneumonia.

Methods

The ICTuS-L trial methodology has been described (Guluma, 2006) and the results have been published (Hemmen *et al.*, 2010). In brief, acute stroke patients aged 18 to 80 were randomized to receive normothermia or hypothermia and an antishivering regimen after intravenous rt-PA according to NINDS guidelines (Group, 1995). ICTuS-L included patients treated with rt-PA within 3 hours or between 3 to 6 hours and for the present analysis, all patients randomized to hypothermia were combined. Patients were cooled with an endovascular cooling catheter (Accutrol™ cooling catheter; Celsius Control Console™; Philips/Innercool, Inc.) placed in the inferior vena cava via a femoral vein sheath. Cooling began as soon as the catheter was placed; the cooling rate was at maximum until the target temperature was reached. The antishivering regimen included: a bolus of 1 mg/kg intravenous meperidine over 10 minutes followed by an infusion of 25 mg meperidine per hour; buspirone 30 mg orally at initiation of cooling followed by 15 mg orally every 8 hours; and a warming blanket placed over the patient set a medium (38°C). If the patient exhibited shivering of any degree, using a validated scale (Badjatia, 2008), the investigator administered additional meperidine (10 or 20 mg) intravenously and adjusted the infusion rate upward in 5 mg/h increments. If the patient appeared to be over sedated, based on the respiratory rate or level of consciousness, the infusion rate was reduced.

For this analysis, we summed the total meperidine used over 24 hours. To summarize the hourly maximum shivering scores over the 24-hour cooling period, we first calculated a total shivering score, as previously described (Lyden, 2012). Temperatures were recorded every hour from a thermistor at the tip of endovascular catheter. To record a temperature, cooling was suspended for 2 minutes to allow thorough mixing of the core venous blood. After a core temperature was taken, cooling resumed.

The target temperature in this trial was 33°C. To estimate total amount of cooling, we then computed the area under the curve (AUC) below the target 34.0, called the AUC34, as previously published (Lyden, 2012). The patient's weight and

height were recorded at enrollment in kilograms and centimeters, respectively. The body mass index (BMI) was estimated using the formula $(\text{weight}/0.0254 \times \text{height})^2$. Age was recorded in years as the patient's age on the date of enrollment. The body surface area (BSA) was calculated as $([\text{weight} \times \text{height}]/3600)^{-2}$.

Statistical analysis

Univariate logistic regression models were used to determine the association between the risk of pneumonia (yes/no) and each of the following variables of interest: age, weight, BMI, BSA, respiration rate, heart rate, blood pressure, baseline National Institutes of Health Stroke Scale (NIHSS), gender, shivering score, AUC below 34°C, and total meperidine dose. Univariate predictors found to be associated with the occurrence of pneumonia at an alpha level of 0.20 were included in a multivariable logistic regression model. Goodness of fit for the final model was assessed using the Hosmer-Lemeshow chi-square statistic. Due to the small sample size overall and the small number of events, testing for the assumption of linearity in the predictors was not performed, and all continuous predictors were treated as continuous variables in the analysis. Also, due to the limited sample available, which precluded stepwise procedures, we focused the multivariable analyses on prespecified hypotheses. Statistical analysis was performed using the statistical software R (version 2.14.0) (www.r-project.org).

Results

In ICTuS-L, pneumonia occurred in 14/28 (50%) patients randomized to receive hypothermia and in 3/30 (10%) of the control group ($p=0.001$). The pneumonia rate did not significantly adversely affect 3-month mRS ($p=0.32$). Although we randomized 28 patients to receive hypothermia, in 2 patients no cooling began due to catheter placement failure or console failure. We used the remaining 26 patients for this analysis. The baseline and outcome variables are summarized in Table 1. There was some collinearity in this dataset; weight and age were modestly inversely correlated ($r=-0.36$, $p=0.07$), meperidine correlated with shivering ($r=0.61$, $p<0.01$), and BSA correlated with weight ($r=0.97$, $p<0.01$), and BMI ($r=0.72$, $p<0.01$). Univariate analyses are summarized in Table 2.

TABLE 1. SUMMARY OF DEMOGRAPHIC VARIABLES

	Mean	SD	Min	Q1	Median	Q3	Max
Age (years)	68.89	8.12	55	61.5	69.5	75.5	80
Weight (kg)	80.66	15.67	51.1	68.5	78.5	93.63	114
BMI (kg/m ²)	28.91	5.66	20.41	24.92	27	30.75	40.32
BSA (m ²)	1.94	0.21	1.47	1.81	1.91	2.09	2.36
Meperidine (mg)	1227	436	295	933	1270	1542	2154
Shivering score	11.85	10.66	0	4.25	8	16.25	38
AUC below 34°C	433	453	0	12.93	246	855	1227
Baseline NIHSS	14.04	5.05	7	10.25	13	17.5	24
Baseline respiration rate	17.48	5.21	12	14	16	20	37
Heart rate	81.15	15.93	54	71.25	79	90	114
Systolic blood pressure	151.1	22.83	107	135.3	151.5	168	188
Diastolic blood pressure	80.42	15.08	48	71.25	80	92	105

See methods for definitions.

AUC, area under the curve; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; BSA, body surface area.

TABLE 2. SUMMARY OF UNIVARIATE ANALYSES

Outcome	Variable	r ²	P
Pneumonia (yes/no)	Age	0.0863	0.2013
	Weight	0.0409	0.3768
	BMI	0.1051	0.1709
	BSA	0.0258	0.4898
	Baseline NIHSS	0.1472	0.1045
	Meperidine	0.0029	0.8112
	AUC below 34	0.0385	0.3888
	Shivering	0.0163	0.5762
	Respiration rate	0.1044	0.2209
	Heart rate	0.0003	0.9400
	Systolic blood pressure	0.0080	0.6941
	Diastolic blood pressure	0.0007	0.9050

Pneumonia risk was not significantly influenced by any single variable. Based on a prespecified alpha of 0.20, two variables qualified for inclusion in the multivariable model, BMI (univariate OR: 0.90, 95% CI: 0.77–1.05, $p=0.171$), and baseline NIHSS (univariate OR: 1.16, 95% CI: 0.97–1.39, $p=0.105$). In the final model (Table 3), neither variable emerged as independently significant, although there was a borderline association between baseline NIHSS and pneumonia risk (OR: 1.19, 95% CI: 0.98–1.43, $p=0.074$), with a Goodness of Fit AUROC of 0.74 ($p=0.06$).

Discussion

Our data reveal that no particular baseline risk factor could be related to the pneumonia risk during endovascular therapeutic hypothermia for acute ischemic stroke. This startling result fails to confirm our hypothesis that meperidine use may have promoted pneumonia in previous studies. In univariate analyses, only baseline stroke severity (NIHSS) weakly appeared to increase risk, a finding seen by others in stroke patients (Hilker, 2003; Aslanyan, 2004; Ovbiagele, 2006; Sellars, 2007). Greater stroke severity may promote pneumonia via impaired protective airway reflexes, increased likelihood of aspiration, impaired respiration, or central immune suppression. BMI, but not weight or BSA, appeared related to lower risk, but this result was not statistically significant. Inasmuch as no prior study has revealed a decreased pneumonia risk in patients with larger BMI, nor can we postulate a protective mechanism of a larger body mass, we suspect this result may be spurious.

Previously, we showed that weight (but not BMI) influenced both the time to reach the cooling target and the total time spent within the target range (Lyden, 2012). Older patients reached the target temperature more quickly consistent with known

impairment of temperature regulation in the aged (Vassilief, 1995). Shivering and resultant meperidine use affected cooling effectiveness independently of the weight effects. From these previous studies, we evolved a concept called “permissive hypothermia”: patients are allowed to reach a target temperature quickly by increasing the meperidine dose (30 mg minibolus and adjust rate upward), but if the respiratory effort appears compromised, no further adjustments are made. Shivering is then controlled by raising the target temperature. The present analysis, by failing to demonstrate an association between meperidine and pneumonia risk, partially calls into question the logic behind permissive hypothermia.

Our study suffers several limitations, however, that may have precluded a positive risk association to meperidine use. The sample size is small and did not allow a rigorous, stepwise variable selection. Many variables, again due to sample size and few events, could not be tested for linearity in the odds of an outcome; all continuous variables were included as continuous rather than categorized variables. Very importantly, in ICTuS-L, the site investigators reported pneumonia without any guidance for systematic observation. As a safety protocol, the ICTuS-L protocol directed the sites to monitor each hypothermia patient continuously and report all observed adverse events; less monitoring of the normothermic patients occurred. Worse, no definition of pneumonia was given and sites may have used clinical, radiographic, or other unknown criteria for concluding a patient suffered pneumonia. Diagnostic accuracy for pneumonia is notoriously poor, even among pulmonary and critical care experts (Hilker, 2003; Naidech, 2012).

The most important lesson of ICTuS-L for preventing pneumonia during hypothermia may be that careful monitoring and prespecified diagnostic criteria are mandatory; these guidelines have been added to the ICTuS 2 protocol currently ongoing. While we continue to hypothesize that permissive hypothermia—through less aggressive titration of the meperidine—should minimize the risk of pneumonia, the present analysis does not support a relationship between meperidine use and pneumonia risk. Other modifications to the ICTuS 2 protocol, designed to minimize pneumonia, may also reduce the risk, perhaps, in combination with less aggressive use of meperidine to control shivering.

Alternatively and importantly, shivering must be controlled to reach the target temperature; shivering increases the metabolic rate and worsens the outcome (Macintyre, 1987). We showed previously that the most important determinant of effective cooling is shivering control with meperidine (Lyden, 2012), with some contribution of baseline factors, including weight and to a lesser extent age. Taking together both the previous and the present findings, the following conclusions emerge: First, shivering control must begin early and continue aggressively to promote rapid cooling to the target temperature. While meperidine does not appear in the present analysis to promote pneumonia risk, this result remains to be proven in larger trials and meperidine rates should not be pushed beyond the earliest signs of respiratory suppression. If shivering continues despite maximally tolerated meperidine, the target temperature must be raised.

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TABLE 3. MULTIVARIABLE ANALYSES OF THE TESTED VARIABLES

	Variable	Estimate	Standard error	z-Value	p
Pneumonia	(Intercept)	1.146	2.781	0.412	0.680
	NIHSS	0.172	0.096	1.786	0.074
	BMI	−0.113	0.091	−1.317	0.188

Hosmer-Lemeshow Goodness of Fit AUROC of 0.74 ($p=0.06$).

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Disclosure Statement

All authors declare that no competing financial interests exist.

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