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The incidence of ARDS and associated Mortality in severe TBI utilizing the Berlin Definition

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Abstract

Background—The incidence of ARDS in severe TBI is poorly reported. Recently a new definition for ARDS was proposed: the Berlin Definition. The percentage of patients represented by TBI in the Berlin criteria study is limited. This study describes the incidence and associated mortality of ARDS in TBI patients.

Methods—The study was an analysis of the safety of erythropoietin administration and transfusion threshold on the incidence of ARDS in severe TBI patients. Three reviewers independently assessed all patients enrolled in the study for ALI/ARDS using the Berlin and the AECC definitions. A Cox proportional-hazards model was used to assess the relationship between ARDS and mortality and 6 month GOS.

Results—Two hundred patients were enrolled in the study. Twenty one percent (41/200) and 26% (52/200) of patients developed ARDS using the AECC and Berlin definitions respectively with a median time of 3 (interquartile range=3) days after injury. ARDS by either definition was associated with increased mortality (p=0.04) but not with differences in functional outcome as measured by the GOS at 6 months. Adjusted analysis utilizing the Berlin criteria showed an increased mortality associated with ADS (p=0.01)

Conclusion—Severe TBI is associated with an incidence of ARDS ranging from 20-25%. The incidence is comparable between the Berlin and AECC definitions. ARDS is associated with increased mortality in severe TBI patients but further studies are needed to validate these findings.

Level of Evidence—Level II, Epidemiological

Keywords

Traumatic Brain Injury; Acute Respiratory Distress Syndrome; Acute Lung Injury

Background

Traumatic Brain injury (TBI) is a major cause of disability and mortality among individuals in both developed and developing countries[1] The acute respiratory distress syndrome (ARDS) and the less severe pulmonary dysfunction, acute lung injury (ALI), are well-described complications of patients who survive the initial traumatic insult. The worldwide incidence of ALI/ARDS in severe TBI has been reported to range from 20% to 30% and subsequent mortality ranges from 28-38%[2-4] However, the majority of previous reports are from retrospective or subgroup analysis[3,5-9] which have significant limitations in accurately identifying ARDS and associated mortality in severe TBI patients. Furthermore, the variation in incidence and outcomes is likely multifactorial and likely impacted by the definition of ALI/ARDS. Consequently, the impact of ALI/ARDS on severe TBI mortality still remains unclear.

ARDS was originally described by Ashbaugh, et al. in 1967[10]. The American-European Consensus Conference (AECC)[11] provided the first consistent definition for ARDS in 1994. The AECC definition was the first structured definition for ARDS but concerns of its

reliability and validity have emerged[12], which has led to the recent ARDS Berlin definition (Table 1) in 2012.[12] The updated Berlin criteria are meant to address the limitations of the AECC criteria.

An accurate description of ALI/ARDS incidence, predictors, and impact on neurologic functioning is important for clinicians to implement the results of clinical trials in the most appropriate patient population as well as for prognosis and resource allocation. We report the incidence of ARDS and its association with mortality and long-term outcome from a recently completed randomized controlled trial of erythropoietin in the severe TBI population using the newly developed Berlin criteria.

Methods

Study Population

We examined data from the 200 patients enrolled in the Erythropoietin TBI trial[13]. Briefly, patients with severe brain injury, the motor component of the Glasgow Coma Score (GCS) <5, at least 15 years of age, and enrolled within 6 hours of injury were recruited at two sites in Houston, Texas. Patients were excluded if their Glasgow Coma Scale score was 3 with fixed and dilated pupils, or if they had penetrating trauma, life-threatening systemic injuries, severe preexisting disease, or were pregnant. After enrollment, patients were randomly assigned to Erythropoietin or placebo and the 7 g/dl or the 10 g/dl transfusion threshold in a 2 × 2 factorial design. Local IRB approval was obtained from the participating sites.

Classification of ARDS

Serial blood gases, ventilatory settings, and serial images of the chest x-rays of the 200 patients were presented to three physicians (a pulmonary critical care physician, a neurocritical care physician, and a trauma surgeon). The physicians, blinded to the trial outcomes and the randomized group assignments, were asked to independently review the cases and determine the pulmonary diagnosis using the AECC and Berlin definitions of ARDS. Using the AECC definition the possible classifications were ‘ARDS’ or ‘no ARDS’ and using the Berlin definition the possible classifications were ‘none’, ‘mild’, ‘moderate’, or ‘severe’ ARDS. At least two physicians were required to agree to obtain a consensus diagnosis for each case.

Outcomes

The primary outcome was the incidence of ARDS by the AECC and the Berlin definitions. The initial study design used the AECC criteria; however, the Berlin criteria was introduced during the study period and therefore the Berlin and AECC criteria were applied to all patients. Secondary outcomes included mortality (within 6 months after injury) and the Glasgow Outcome Scale (GOS) score obtained by a structured interview at 6 months post injury. Although all patients were examined for the presence of ARDS using the both criteria we focused on the Berlin criteria for our secondary outcomes.

Statistical Methods

In the original trial, there were no differences in the incidence of ARDS detected between the erythropoietin and placebo groups and between the transfusion threshold groups; thus, pooled analysis of the groups were performed.[13] Baseline characteristics among those who did and did not develop incident ARDS were compared using either a Fisher's exact test for categorical variables or a Wilcoxon rank sum test for continuous variables. Multivariable analysis of risk factors for ARDS was assessed using the Cox proportional hazards model. Lasso-penalized Cox regression, with the penalty parameter selected by 5-fold cross-validation, was used for variable selection.[14] The proportional hazards assumption was assessed using Schoenfeld residual plots and testing for interaction terms with time. Fisher's exact test was used to assess the association between ARDS and each of the two secondary outcomes, GOS and mortality. A Cox proportional-hazards model was used to assess the relationship between time-dependent incidence of ARDS and mortality, adjusting for fixed-time covariates transfusion threshold group, EPO treatment group, injury severity score, and IMPACT predicted probability of death. The type I error rate (or alpha level) was set at 0.05.

Results

A total of 200 patients were included in the analysis. There were no instances where consensus was not achieved. Twenty one percent (41/200) and 26% (52/200) of patients developed ARDS using the AECC and Berlin definitions respectively with a median time of 3 (interquartile range=3) days after injury. When the mild ARDS group was removed from the Berlin criteria group, the incidence was almost identical, 20% (38/200) and 21% (41/200) in the Berlin and AECC criteria, respectively. The median tidal volume for all 128 patients with this measure was 8.94mL/kg (25^{th} and 75^{th} percentiles, 8.22mL/kg and 9.76mL/kg respectively) prior to the development of ARDS. Patients clinically were managed using lung protective strategies once ARDS was identified clinically. There were no detectable differences in median tidal volume between the ARDS and non-ARDS groups irrespective of ARDS criteria. Demographic and baseline characteristics stratified by ARDS using the Berlin criteria are shown in Table 2. Acuity of illness, as defined by APACHE II and AIS, was associated with incident ARDS ($p \leq 0.01$). Initial ER summary GCS was statistically different between those with and without ARDS (p=0.02). However, this difference (GCS 6 vs. GCS 7) is not clinically significant. There were statistically significant differences between the ARDS and non-ARDS groups with respect to male sex and pre hospital hypoxia. The population was 96.2% male in the ARDS group and 83.1% in the non-ARDS group (p=.03) and instances of pre hospital hypoxia were 30.8% in the ARDS group and 15.5% in the non-ARDS groups (p=.02). In a multivariable model for ARDS development, elevated APACHE II and pre-hospital hypoxia were associated with over a 2-fold increase in the hazard and pre-hospital hypotension was associated with decreased hazard of ARDS (Table 3). The overall mortality in the trial was 15.5% (31/200). Among subjects who developed ARDS, mortality was 25.0% (13/52, 95% confidence interval 14%-39%) (Table 4). ARDS by either definition was associated with increased mortality (p=0.04) but not with differences in functional outcome as measured by the GOS at 6 months (Table 5). In the adjusted Cox proportional-hazards analysis ARDS was found to be associated with an increased risk in mortality (HR: 2.560; p=0.01) (Table 6).

Discussion

Severe TBI has been associated with ARDS in previous literature. The incidence has varied significantly in different reports and over time. In one retrospective cohort of patients over a 20-year period, the prevalence of ARDS/ALI increased from 2% to 22% and mortality decreased from 13% to 9%.[5] Severe TBI and ARDS carries a significant mortality and valid, reliable definitions of ALI and ARDS are essential to conduct epidemiological studies successfully and for evaluating outcomes related to TBI and ALI/ARDS. This study was initiated using the AECC criteria. We evaluated all patients using both the AECC and the Berlin criteria and reported the first prospective and comparative evaluation of the two criteria in severe TBI patients. The incidence of ARDS was similar but slightly higher using the Berlin definition. It is important to note that exclusion of the mild ARDS criteria from the Berlin definition group, which by PaO2/FiO2 ratio is similar to the ALI group in the AECC definition, yields virtually identical incidences. The incidence of ARDS in our study population is consistent with previous reports with ranges from 20-30% irrespective of which criteria are utilized.

The AECC definition was widely adopted by clinicians (Table 1).[11,15] The new criteria are very similar to prior criteria with respect to timing, chest imaging, origin of edema, and degree of hypoxemia.[12] The differences are highlighted in Table 1. The term ALI was removed and different levels of ARDS were defined to better categorize patients with respect to severity of disease and lung injury and provide a better predictive model for mortality[15]. The Berlin criteria were associated with increased mortality and increased median duration of mechanical ventilation when tested in 4188 patients with ARDS from 4 multicenter clinical data sets.[12,16-19] The applicability of this cohort to severe TBI is questionable. Although 3 of the 4 studies that comprise the patient population for the Berlin criteria meta-analysis reported trauma as etiology for ARDS, none of the studies differentiate between systemic trauma and TBI. Trauma represented approximately 6% or 250 of the over 4000 patients reported and severe TBI would likely represent an even smaller number. There are conflicting reports in the literature of ARDS as an independent predictor of mortality. One prospective trial of 137 severe TBI patients showed increased mortality and worse long term neurologic outcome in the ALI/ARDS group in contrast to a separate retrospective evaluation of 362 severe TBI patients that showed no difference in mortality or disability at discharge.[3,7] ARDS was associated with mortality in our cohort. The incidence of ARDS and associated mortality in our population is more consistent with Holland's prospective trial. These two trials represent the only prospective evaluation of ARDS and mortality in severe TBI patients. Our cohort represents one of the largest prospective studies of severe TBI and ARDS and the first to describe the incidence and mortality using the Berlin criteria.

While severe TBI is known to have an increased risk of ARDS, we did not identify any baseline characteristics or clinical variables that were associated with ARDS except for severity of illness, male sex, and pre-hospital hypoxia. Several studies have demonstrated the importance of high tidal volume ventilation in the etiology and the therapeutic benefits of low tidal volume ventilation as a therapeutic strategy (ARDS Net, plus). The ARDSNet trial [20] demonstrating the impact of lower tidal volume on mortality in ARDS patients was

published prior to the initiation of our trial. Data showing the tidal volume per predicted body weight in TBI patients was not presented in that trial. In our trial we found there was no detectable difference in tidal volume between the two groups and all patients were ventilated at less than 10cc/kg IBW. This likely represents a trend towards lower tidal volume ventilation strategies for all patients. The mechanism of injury, the radiographic classification of injury, or the need for surgery was not associated with ARDS either.

Severe TBI is associated with an incidence of ARDS ranging from 20-25% and severity of illness may be the most significant predictor of ARDS. ARDS is associated with increased mortality but further studies are needed to validate these findings. Comparison of the Berlin and the AECC definitions did not yield significant differences in incidence or associated mortality attributable to ARDS in severe TBI patients. The lack of statistically significant differences between ARDS diagnostic criteria affirms previous published data on the incidence of ARDS and more importantly allows for comparison of ARDS in future studies with past studies in severe TBI patients.

We suggest future studies using the Berlin criteria may be compared against previous reports using the AECC definition but include the ALI group to represent the mild ARDS patients.

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Table 1
North American European Consensus Conference and Berlin Definition

AECC Definition	Berlin Definition
1. Acute Onset	1. Acute Onset within 7 days
2. Bilateral pulmonary infiltrates consistent with pulmonary edema	2. Bilateral pulmonary infiltrates consistent with pulmonary edema
3. Impaired oxygenation: PaO2/FiO2 ratio < 300 mm Hg → ALI PaO2/FiO2 ratio < 200 mm Hg → ARDS	3. Impaired Oxygenation PaO2/FiO2 ratio 200 – 300 mm Hg → mild PaO2/FiO2 ratio 100 – 200 mm Hg → moderate PaO2/FiO2 ratio < 100 mm Hg → severe
4. No evidence of left heart failure PAWP ≤ 18	4. Impaired oxygenation not fully explained by cardiac failure

Table 2
Baseline Characteristics of the Study Participants using Berlin criteria

Characteristic	Developed ARDS (N=52)	Did not develop ARDS (N=148)	p-value
Transfusion threshold <10 g/dL, n (%)	28 (53.8)	73 (49.3)	0.63
Age (yr), median (IQR)	29.0 (19.5)	30.0 (23.0)	0.87
Male sex, n (%)	50 (96.2)	124 (83.8)	0.03
Race, n (%)			
Black	8 (15.4)	35 (23.6)	0.44
White	16 (30.8)	32 (21.6)	
Hispanic	27 (51.9)	76 (51.4)	
Asian	1 (1.9)	5 (3.4)	
ER sum GCS			
>8	7 (13.5)	38 (25.7)	0.04
6-8	21 (40.4)	68 (45.9)	
3-5	24 (46.2)	42 (28.4)	
ER sum GCS, median (IQR)	6.0 (5.0)	7.0 (4.0)	0.02
Marshall Classification on CT			
mild diffuse injury	23 (44.2)	66 (44.6)	0.22
severe diffuse injury	16 (30.8)	30 (20.3)	
mass lesion	13 (25.0)	52 (35.1)	
APACHE II, median (IQR)	24.0 (11.0)	19.0 (7.0)	<0.003
Abbreviated Injury Severity Score, median (IQR)	32.0 (14.5)	28.0 (10.0)	0.01
Intracranial Pressure (n=197), n (%)	14.0 (12.0)	14.0 (12.0)	0.84
Mechanism of Injury, n (%)			
Assault	7 (13.5)	15 (10.1)	0.93
Fall/Jump	7 (13.5)	20 (13.5)	
Motor Vehicle	28 (53.8)	88 (59.5)	
Motorcycle	9 (17.3)	22 (14.9)	
Other	1 (1.9)	3 (2.0)	
Surgery on admission, n (%)	13 (25.0)	48 (32.4)	0.38
Pre-hospital hypotension, n (%)	7 (13.5)	18 (12.2)	0.81
Pre-hospital hypoxia	16 (30.8)	23 (15.5)	0.02
Time (days) from injury to ALI, median (IQR)	3.0 (3.0)		

Table 3
Multivariable Cox Proportional Hazards Model of Risk Factors of ARDS

	HR	95% Confidence Interval	P value
Transfusion threshold <10 g/dL	1.14	0.65-2.01	0.648
Male sex	3.69	0.88-15.38	0.073
Apache II ≤16 (reference)			
(16-20]	0.54	0.20-1.41	0.206
(20-25]	1.47	0.64-3.38	0.364
>25	2.73	1.21-6.14	0.015
Abbreviated Injury Severity Score	1.02	0.97-1.06	0.474
Surgery on Admission	0.69	0.36-1.33	0.268
Pre-hospital Hypoxia	2.08	1.13-3.83	0.018
Pre-hospital Hypotension	0.42	0.18-0.99	0.048
Abbreviated Injury Severity - Thorax	1.25	0.59-2.67	0.565

Table 4
Definition of ARDS/ALI and mortality following an ARDS event

ALI/ARDS Criteria	All-cause Mortality
Berlin Criteria	13/52 (25.0%)
a. Mild ARDS (PaO2/FIO2 200 - 300 mm Hg), n (%)	2/11 (18.2)
b. Moderate ARDS (PaO2/FIO2 100 - 200 mm Hg), n (%)	3/27 (11.1)
c. Severe ARDS (PaO2/FIO2 ≤ 100 mm Hg), n (%)	8/14 (57.1)

Table 5

Association of developing incident ARDS (based on the Berlin criteria) with GOSS at 6 months and with mortality

	No ARDS	ARDS	*P* value
GOSS at 6 months, n			0.39
Unfavorable	87	35	
Favorable	53	15	
Death, n			0.04
Did not die	130	39	
Died	18	13	

Table 6

Cox Regression Analysis –Mortality and time-dependent Incidence of ARDS adjusted for fixed-time Pre-specified Covariates

Mortality	Hazard Ratio	95% Confidence Interval	p-value
Incidence of ARDS	2.56	1.21 -5.43	0.01
Epo1 regimen (compared to Placebo)	0.98	0.36-2.67	0.97
Epo2 regimen (compared to Placebo)	0.86	0.34-2.15	0.74
Transfusion Threshold <10 g/dL (compared to TT7)	0.99	0.47-2.06	0.97
Injury Severity Score	1.01	0.97-1.05	0.74
IMPACT probability of Death	1.05	1.03-1.07	<.001