Effect of Different Early Oxygenation Levels on Clinical Outcomes of Patients Presenting in the Emergency Department With Severe Traumatic Brain Injury

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Study objective: Despite the almost universal administration of supplemental oxygen in patients presenting in the emergency department with severe traumatic brain injury, optimal early oxygenation levels are unknown. Therefore, we aimed to examine the effect of different early oxygenation levels on the clinical outcomes of patients presenting in the emergency department with severe traumatic brain injury.

Methods: We performed a secondary analysis of the Resuscitation Outcomes Consortium Traumatic Brain Injury Hypertonic Saline randomized controlled trial by including patients with Glasgow Coma Scale $\leq$8. Early oxygenation levels were assessed by the worst value of arterial partial pressure of oxygen (PaO_2) during the first 4 hours of presentation in the emergency department. The primary outcome was 6-month neurologic status, as assessed by the Extended Glasgow Outcome Scale. A binary logistic regression was utilized, and an odds ratio (OR) with 95% (95% confidence intervals) was calculated.

Results: A total of 910 patients were included. In unadjusted (crude) analysis, a PaO_2 of 101 to 250 mmHg (OR, 0.59 [0.38 to 0.91]), or 251 to 400 mmHg (OR, 0.53 [0.34 to 0.83]) or $\geq$401 mmHg (OR, 0.31 [0.20 to 0.49]) was less likely to be associated with poor neurologic status when compared with a PaO_2 of $\leq$100 mmHg. This was also the case for adjusted analyses (including age, pupillary reactivity, and Revised Trauma Score).

Conclusion: High oxygenation levels as early as the first 4 hours of presentation in the emergency department may not be adversely associated with the long-term neurologic status of patients with severe traumatic brain injury. Therefore, during the early phase of trauma, clinicians may focus on stabilizing patients while giving low priority to the titration of oxygenation levels. [Ann Emerg Med. 2022;■:1-9.]

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INTRODUCTION

Background and Importance

Traumatic brain injury is an important cause of death and disability worldwide.[1] Even more disturbing, traumatic brain injury-related emergency department visits increased by 70% from 2001 to 2010, justifying the characterization of traumatic brain injury as an ever-increasing "silent epidemic."[2] Despite the impressive epidemiology, medical research on managing traumatic brain injury as opposed to other health problems is underrepresented.[3] Consequently, there are few data to support commonly used interventions for managing traumatic brain injury, especially in the emergency department setting. For example, despite the almost universal usage of supplemental oxygen in patients presenting in the emergency department with severe traumatic brain injury, optimal early oxygenation levels are unknown.

On the one hand, there are arguments for high oxygenation levels. It has been found that reduced cerebral oxygenation after brain injury may be associated with an increased risk of secondary brain damage mediated by impaired mitochondrial function and metabolism,[4] whereas short administration of high oxygen levels was associated with improved cerebral metabolism.[5] Based on the above findings, along with the perception that liberal usage of oxygen may provide a margin of safety against hypoxemia, one could advocate high oxygenation levels in patients with traumatic brain injury. On the other hand, there are increasing concerns that excessive oxygenation levels have harmful effects, such as central nervous system toxicity, cerebral vasoconstriction, impaired immunity leading to a predisposition to infections (including pneumonia), and acute lung injury/acute respiratory

Editor's Capsule Summary

What is already known on this topic

While low values are known to be harmful, the best early target for arterial oxygen levels in comatose patients after traumatic brain injury is unclear.

What question this study addressed

How do early arterial oxygen levels impact neurological outcomes?

What this study adds to our knowledge

In a secondary analysis of 910 patients enrolled in a traumatic brain injury care trial, higher arterial oxygen levels (PaO_2>100 mmHg), including very high values (PaO_2>400 mmHg), in the first 4 hours after arrival were associated with lower mortality and better 6-month neurological recovery compared to low arterial oxygen levels (PaO_2 below 100 mmHg).

How this is relevant to clinical practice

In comatose traumatic brain injury patients, these data support an initial PaO_2>100 mmHg target and not fearing hyperoxemia early in resuscitation.

distress syndrome.[6,7] Taken together, there are theoretical risks and merits for different oxygenation levels.

Guidance on the optimal oxygenation levels in patients with traumatic brain injury is limited. In its relevant best practice guidelines, the American College of Surgeons recommended arterial partial pressure of oxygen (PaO_2) above 100 mmHg without specifying an upper oxygenation limit.[8] The latest relevant guidelines from the Brain Trauma Foundation and the World Society of Emergency Surgery make no recommendations stressing the need for additional research on the subject.[9,10]

Goals of This Investigation

Considering the above considerations, we took advantage of data from a large Resuscitation Outcomes Consortium randomized controlled trial to examine the association between different early oxygenation levels and important clinical outcomes, including long-term neurologic status, of patients presenting in the emergency department with severe traumatic brain injury. Specifically, in this secondary analysis of a randomized controlled trial, we hypothesized that high oxygenation levels as early as the first 4 hours of presentation in the emergency department may not be adversely associated with the long-term neurologic status of patients with severe traumatic brain injury.

MATERIALS AND METHODS

Study Design, Setting, and Selection of Participants

We performed a secondary analysis using data from the Traumatic Brain Injury Hypertonic Saline randomized controlled trial conducted by the Resuscitation Outcomes Consortium.[11] We were granted access to trial data from the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung and Blood Institute following the submission of a protocol.[12] Full details of the trial have been published.[11] Briefly, the Resuscitation Outcomes Consortium Traumatic Brain Injury Hypertonic Saline trial enrolled 1,282 (out of the 1,331 initially randomized) patients aged 15 years or older with blunt trauma and an out-of-hospital (ie, before their presentation in the emergency department) Glasgow Coma Scale ≤8 who did not meet criteria for hypovolemic shock. Subjects were randomized to receive either hypertonic saline/dextran (intervention group) or normal saline (control group), and no difference was revealed between groups in terms of long-term neurologic status and mortality. In the Resuscitation Outcomes Consortium Traumatic Brain Injury Hypertonic Saline trial, data on PaO_2 were collected from patients with traumatic brain injury within 4 hours of their presentation in the emergency department.[11] We took advantage of the latter fact (availability of data on different early oxygenation levels) to perform the current secondary analysis. Therefore, the current secondary analysis, which was approved by the institutional review board of Evangelismos Hospital (protocol number 431/2021), included adult patients presenting in the emergency department with severe traumatic brain injury (ie, patients who continued to have Glasgow Coma Scale ≤8 during their presentation in the emergency department) and for whom the worst PaO_2 value within 4 hours of presentation in the emergency department was available.

Based on the worst PaO_2 value, we considered 4 oxygenation groups, namely PaO_2≤100 mmHg, PaO_2=101 to 250 mmHg, PaO_2=251 to 400, and PaO_2≥401 mmHg. We considered 4 rather than only 2 oxygenation groups in an attempt to detect possible nonlinear associations between oxygenation levels and clinical outcomes. We determined these groups based on the distribution of oxygenation levels in the study population and on recommendations that PaO_2 should be maintained above 100 mmHg.[8]

Outcome Measures

The primary outcome of the secondary analysis was 6-month neurologic status based on the Extended Glasgow

Outcome Scale (GOS-E).[13] Similar to the original trial,[11] the GOS-E score was dichotomized into good outcome (namely, moderate disability or good recovery; GOS-E >4) and poor outcome (namely, death, vegetative state, or severe disability; GOS-E≤4).

The secondary outcomes of the secondary analysis were all-cause mortality, development of acute respiratory distress syndrome, and development of nosocomial pneumonia, all within 28 days from trial enrollment. We chose the development of acute respiratory distress syndrome because high oxygenation may be associated with lung injury.[14] Also, we chose the development of nosocomial pneumonia because pneumonia is the most common infection of patients with traumatic brain injury and is independently associated with an approximately 7-fold increase in odds of lower functional outcomes scores.[15]

Primary Data Analysis

Frequencies, percentages, medians (interquartile ranges), and odds ratios (OR) with 95% confidence intervals (95% CI), as well as forest plots, were used for data presentation.

Binary logistic regression was utilized to study the effect of oxygenation levels (assessed by PaO_2 values) on primary and secondary outcomes. PaO_2≤100 mmHg was utilized as a "reference" category to calculate OR. For the primary outcome analysis, 3 models are presented. Our first "crude (unadjusted)" model includes PaO_2. The second "basic" model includes PaO_2, age, pupillary reactivity, and Revised Trauma Score. The third "full" model includes variables of the basic model, plus admission hemoglobin, and Marshall Computed Tomography (CT) classification score, and Injury Severity Score. To select the above-mentioned variables, we considered the IMPACT investigators' relevant work on prediction models among patients with moderate-to-severe traumatic brain injury (Glasgow Coma Scale≤12).[16] In their basic model,[16] the IMPACT investigators included age, pupillary reactivity, and motor component of the Glasgow Coma Scale. Likewise, our "basic" model included age, pupillary reactivity, and Revised Trauma Score. We had to consider the Revised Trauma Score (a score heavily weighted toward the Glasgow Coma Scale) rather than the motor component of the Glasgow Coma Scale because most patients included in our analysis of severe traumatic brain injury had a motor component of Glasgow Coma Scale equal to 1, which did not allow for proper categorization.[17] With regard to our "full" model, our selected variables (namely, admission hemoglobin and Marshall CT classification score) had been previously identified as important by the IMPACT investigators.[16] Apart from the above-mentioned variables, we considered in our "full" model the Injury Severity Score,[18] with the rationale being that severity of injuries in total, and especially of the chest, may affect the ability of patients to properly oxygenate.

Each of the above-mentioned models was constructed using all available information on the included variables and outcomes, and (Table E1, available online at http://www.annemergmed.com) shows the missing values. In addition to the above approach of removing cases with missing values from each model, we addressed missingness by performing a sensitivity analysis with multiple imputations. We imputed 10 datasets of baseline characteristics and outcomes and pooled the results. Two more sensitivity analyses of the primary outcome were performed; namely, 1 analysis after excluding moribund patients (ie, patients who died in the first 24 hours) and another analysis after including into the above-mentioned "full" model the variable "out-of-hospital intubation." We considered the latter variable because out-of-hospital intubation may be a surrogate for injury severity and/or may affect oxygenation levels (intubated patients may be able to receive a higher fraction of inspired oxygen and, therefore, may have higher PaO_2 than nonintubated patients).

Statistical analyses were performed using SPSS software version 26.0 (IBM, Armonk, NY). Forest plots were created using GraphPad Prism version 9.0.0 (GraphPad Software, La Jolla, CA). Point and interval estimates (OR with 95% CI) rather than *P* values were utilized to present the main study results.[19]

RESULTS

Characteristics of Study Subjects

Figure E1, available online at http://www.annemergmed.com, shows the patient flow diagram for the present secondary analysis. Out of 1,282 patients enrolled in the Resuscitation Outcomes Consortium Traumatic Brain Injury Hypertonic Saline trial, 1,037 patients continued to have a Glasgow Coma Scale ≤8 during their presentation in the emergency department. Of those 1,037 patients, 910 had a PaO_2 value available within 4 hours of their presentation in the emergency department, whereas 127 patients missed such a PaO_2 value. Table E2 shows the baseline characteristics of the 127 excluded patients (without PaO_2) and the 910 included patients (with PaO_2).

Therefore, 910 patients who continued to have a Glasgow Coma Scale ≤8 during their presentation in the emergency department and also had a PaO_2 value available within 4 hours of their presentation in the emergency department were included in the current secondary

analysis. Table 1 shows baseline characteristics of included patients categorized by early oxygenation level, namely $PaO_2 \leq 100$ mmHg (178 patients), $PaO_2 = 101$ to 250 mmHg (280 patients), $PaO_2 = 251$ to 400 (241 patients), and $PaO_2 \geq 401$ mmHg (211 patients). In addition, the group of patients with $PaO_2 \leq 100$ mmHg had higher Injury Severity Score, were less likely to have both pupils reactive, and had lower admission hemoglobin than compared groups (Table 1).

Main Results

Table 2 shows the association between different early oxygenation levels and the primary outcome (namely, 6-month neurologic status based on GOS-E). In unadjusted (crude) analysis, a PaO_2 of 101 to 250 mmHg (OR 0.59 [0.38 to 0.91]), or 251 to 400 mmHg (OR 0.53 [0.34 to 0.83]), or ≥401 mmHg (OR 0.31 [0.20 to 0.49]) was less likely to be associated with poor neurologic status when compared with a PaO_2 of ≤100 mmHg (Figure 1). Similarly, even after adjusting for age, pupillary reactivity, and Revised Trauma Score ("basic" model), a PaO_2 of 101 to 250 mmHg (OR 0.58 [0.35 to 0.95]), or 251 to 400 mmHg (OR 0.58 [0.35 to 0.98]), or ≥401 mmHg (OR 0.39 [0.23 to 0.67]) was less likely to be associated with poor neurologic status when compared with a PaO_2 of ≤100 mmHg (Figure 1). This was also the case after additionally adjusting for admission hemoglobin, Marshall CT classification score, and Injury Severity Score ("full" model); ie, for the comparison of a PaO_2 of 101 to 250 mmHg (OR 0.87 [0.49 to 1.52]), or 251 to 400 mmHg (OR 0.75 [0.42 to 1.35]), or ≥401 mmHg (OR 0.57 [0.31 to 1.05]) with a PaO_2 of ≤100 mmHg (Figure 1). Table E3 shows the contribution of each of the above-mentioned variables other than PaO_2 (namely, age, pupillary reactivity, Revised Trauma Score, admission hemoglobin, Marshall CT classification score, and Injury Severity Score) to the findings in our "basic" and "full" logistic regression models. The main message also persisted in the sensitivity analysis using multiple imputations (Table E4), in the analysis after excluding 121 patients who died within 24 hours (Figure E2), and in the analysis after including out-of-hospital intubation in the "full" model (Figure E3).

Table 2 shows the association between different early oxygenation levels and the secondary outcomes, namely mortality, development of acute respiratory distress syndrome, and nosocomial pneumonia within 28 days from trial enrollment. A PaO_2 of 101 to 250 mmHg, or 251 to 400 mmHg, or ≥401 mmHg was less likely to be associated with mortality (Figure 2) and acute respiratory distress syndrome (Figure E4), but not nosocomial pneumonia (Figure E5), when compared with a PaO_2 of ≤100 mmHg.

LIMITATIONS

Our secondary analysis has limitations. Firstly, although it was based on high-quality data (including long-term follow-up data) from a large, robust randomized controlled trial,[11] there were missing values both with regard to initial PaO_2 values and 6-month neurologic status. With regard to initial PaO_2 values, we acknowledge that the exclusion of 127 patients who missed such values might introduce selection bias, as shown in Table E2, which presents baseline characteristics and outcomes of the 127 excluded patients (without PaO_2) and the 910 included patients (with PaO_2). With regard to the 6-month neurologic status, we acknowledge that 11% missingness for the total cohort (with differences among oxygenation groups; 10.9% in the group of $PaO_2 \geq 401$ mmHg but 7.3% in the group of $PaO_2 \leq 100$ mmHg), albeit on par with high-quality studies on traumatic brain injury,[20,21] may still be a limitation. To address this limitation, we performed a sensitivity analysis with multiple imputations and found similar results.

Secondly, because of its study design, our analysis was inevitably subjected to confounding. As shown in Table 1, there were differences among oxygenation groups (especially between the group of $PaO_2 \leq 100$ mmHg and the group of $PaO_2 \geq 401$ mmHg) in terms of baseline characteristics, such as age, Glasgow Coma Scale, Injury Severity Score, pH and arterial partial pressure of carbon dioxide ($PaCO_2$). We attempted to adjust for several of the above-mentioned confounders in our "full" model (Figure 1). The "full" model did not include $PaCO_2$ (despite its high association with outcomes of patients with traumatic brain injury)[22] in an attempt to avoid collinearity as we thought that arterial blood gases (namely PaO_2 and $PaCO_2$) might convey closely related information. Despite our efforts, we fully acknowledge that we might overlook other potentially important confounders. For example, the inclusion of the Injury Severity Score in our "full" model might not have adequately addressed the presence of extraaxial injury, which might be presumed by the need for fluid resuscitation and blood transfusion. Taken together, we could not rule out that differences in early oxygenation levels may simply signal differences in characteristics or accompanying injuries of patients, and therefore our study should only be viewed as hypothesis-generating. A randomized controlled trial could establish the

Table 1. Baseline characteristics of included patients categorized by early oxygenation level (as assessed by the arterial partial pressure of oxygen [PaO_2]).

Characteristic	Total (n=910)	≤100 mmHg (n=178)	101 to 250 mmHg (n=280)	251 to 400 mmHg (n=241)	≥401 mmHg (n=211)
Age, y; median [IQR]	33.0 [23.5 to 50.0]	33.0 [23.0 to 51.5]	38.0 [25.3 to 55.0]	36.0 [25.0 to 49.0]	27.0 [21.0 to 43.0]
Female sex, n (%)	210 (23.1)	35 (19.7)	60 (21.4)	56 (23.2)	59 (28.0)
Race, n (%)					
White	484 (53.2)	90 (50.6)	131 (46.8)	134 (55.6)	129 (61.1)
Black	76 (8.4)	18 (10.1)	17 (6.1)	20 (8.3)	21 (10.0)
Asian	36 (4.0)	6 (3.4)	12 (4.3)	10 (4.1)	8 (3.8)
Other/unknown	314 (34.5)	64 (36.0)	120 (42.9)	77 (32.0)	53 (25.1)
Total out-of-hospital time, minutes, median [IQR]	53.4 [40.0 to 69.0]	54.2 [39.0 to 68.2]	54.0 [40.0 to 70.3]	53.8 [40.2 to 68.1]	52.1 [39.8 to 67.9]
Out-of-hospital intubation, n (%)	644 (70.8)	115 (64.6)	191 (68.2)	173 (71.8)	165 (78.2)
Blunt trauma, n (%)	894 (98.2)	177 (99.4)	275 (98.2)	238 (98.8)	204 (96.7)
Glasgow Coma Scale, median [IQR]	3.0 [3.0 to 3.0]	3.0 [3.0 to 3.0]	3.0 [3.0 to 4.0]	3.0 [3.0 to 3.0]	3.0 [3.0 to 4.0]
Revised Trauma Score, median [IQR]	5.0 [4.1 to 6.0]	4.4 [4.1 to 5.7]	4.7 [4.1 to 6.0]	5.0 [4.1 to 6.0]	5.0 [4.1 to 6.0]
Injury Severity Score, median [IQR]	27.0 [18.0 to 38.0]	35.0 [25.0 to 45.0]	27.0 [18.0 to 38.0]	26.0 [17.0 to 37.5]	25.0 [17.0 to 34.0]
Both pupils reactive, n (%)	517 (58.9)	90 (53.3)	145 (53.5)	152 (65.2)	130 (63.4)
Marshall CT classification score > Diffuse injury II, n (%)	343 (38.9)	69 (42.1)	100 (36.5)	96 (40.9)	78 (37.5)
Highest heart rate (beats/min), median [IQR]	110.0 [94.0 to 127.5]	115.0 [96.0 to 133.3]	109.0 [94.0 to 126.0]	108.0 [95.5 to 125.0]	110.0 [94.0 to 128.3]
Lowest systolic blood pressure (mmHg), median [IQR]	110.0 [91.0 to 126.0]	102.0 [80.0 to 124.0]	111.0 [92.8 to 126.0]	112.0 [95.0 to 125.0]	114.0 [99.0 to 128.5]
Worst pH, median [IQR]	7.3 [7.2 to 7.4]	7.2 [7.1 to 7.3]	7.3 [7.2 to 7.4]	7.3 [7.2 to 7.4]	7.3 [7.3 to 7.4]
Worst $PaCO_2$ (mmHg), median [IQR]	42.0 [37.0 to 49.0]	50.0 [44.0 to 58.3]	43.0 [38.0 to 49.0]	41.0 [36.0 to 45.0]	38.0 [35.0 to 43.0]
Hemoglobin (g/dL), median [IQR]	12.8 [11.2 to 14.1]	12.3 [10.6 to 13.7]	13.0 [11.6 to 14.0]	12.8 [11.1 to 14.3]	13.1 [11.3 to 14.2]

IQR, interquartile range; *n,* number.

Table 2. Association between different early oxygenation levels (assessed by arterial partial pressure of oxygen [PaO_2]) and outcomes of included patients.

Outcome	≤100 mmHg	101 to 250 mmHg	251 to 400 mmHg	≥401 mmHg
Poor 6-mo neurologic status (GOS-E ≤4)				
n (%)	123 (74.5)	158 (63.2)	126 (60.9)	90 (47.9)
OR (95% CI), crude model*	Ref	0.59 (0.38 to 0.91)	0.53 (0.34 to 0.83)	0.31 (0.20 to 0.49)
OR (95% CI), basic model†	Ref	0.58 (0.35 to 0.95)	0.58 (0.35 to 0.98)	0.39 (0.23 to 0.67)
OR (95% CI), full model‡	Ref	0.87 (0.49 to 1.52)	0.75 (0.42 to 1.35)	0.57 (0.31 to 1.05)
All-cause mortality				
n (%)	73 (41.2)	77 (27.5)	58 (24.3)	39 (18.6)
OR (95% CI), crude model*	Ref	0.54 (0.36 to 0.80)	0.46 (0.30 to 0.70)	0.32 (0.21 to 0.51)
Acute respiratory distress syndrome				
n (%)	24 (13.5)	13 (4.6)	22 (9.1)	16 (7.6)
OR (95% CI), crude model*	Ref	0.31 (0.15 to 0.63)	0.64 (0.35 to 1.19)	0.53 (0.27 to 1.03)
Nosocomial pneumonia				
n (%)	44 (26.7)	61 (23.0)	53 (22.9)	53 (26.1)
OR (95% CI), crude model*	Ref	0.82 (0.53 to 1.29)	0.82 (0.52 to 1.30)	0.97 (0.61 to 1.55)

CI, Confidence intervals; *n,* number; *Ref,* reference group.
Secondary outcomes (namely, all-cause mortality, acute respiratory distress syndrome and nosocomial pneumonia) were assessed within 28 days from trial enrollment.
*The crude (unadjusted) model includes PaO_2.
†The basic model includes PaO_2, age, pupillary reactivity, and Revised Trauma Score.
‡The full model includes variables of the basic model, plus admission hemoglobin, Marshall CT classification score, and Injury Severity Score.

independent effect of different oxygenation levels on the clinical outcomes of patients with traumatic brain injury.

Thirdly, we lacked data on the exact timing of the blood draw to measure PaO_2, ie, whether it occurred before or after intubation, which might influence the interpretation of our findings. Finally, we also lacked relevant data, allowing us to use more than a single value of "lowest PaO_2" to mark systemic oxygenation and to expand our observation to a period of 4 to 24 hours from presentation in the emergency department.

DISCUSSION

By taking advantage of data from the large Resuscitation Outcomes Consortium Traumatic Brain Injury Hypertonic Saline randomized controlled trial,[11] the present secondary analysis found that when compared with a PaO_2 of ≤100 mmHg, a PaO_2 of 101 to 250 mmHg, or 251 to 400 mmHg, or ≥401 mmHg was less likely to be associated with poor neurologic status, mortality and development of acute respiratory distress syndrome. The above findings, which are based on 910 patients with severe traumatic brain injury, suggest that high oxygenation levels as early as the first 4 hours of presentation in the emergency department may not be adversely associated with clinical outcomes, including long-term neurologic status, of such patients.

Although data exist on the association between oxygenation and outcomes of patients with traumatic brain injury, the present secondary analysis may add to the literature by specifically exploring the optimal oxygenation levels in the early posttrauma phase, ie, in the setting of the emergency department. Our main finding (ie, high early oxygenation levels may not be adversely associated with long-term neurologic status) persisted even after adjusting for several confounders as well as after excluding moribund patients (ie, patients who died within 24 hours). The above-mentioned may denote the robustness of our finding. This finding seems to be in line with results from small studies reporting that low oxygenation levels were associated with worse outcomes of patients with traumatic brain injury.[23,24] Also, our main finding corroborates the result of a study by Fujita et al,[25] which showed that oxygenation levels as early as a mean of 5.6 hours after the onset of traumatic brain injury were higher in patients with favorable versus unfavorable neurologic outcomes.[25]

On the other hand, our main finding (ie, high early oxygenation levels may not be adversely associated with long-term neurologic status) seemingly contradicts the results of other contributions. Indeed, Brenner et al[26] reported that PaO_2 values higher than 200 mmHg, as opposed to 100 to 200 mmHg, within 24 hours from hospital admission were associated with worse neurologic status and higher mortality of patients with traumatic brain injury. Similarly, Alali et al[27] reported that PaO_2 values higher than 200 mmHg, as opposed to 150 to 200 mmHg,

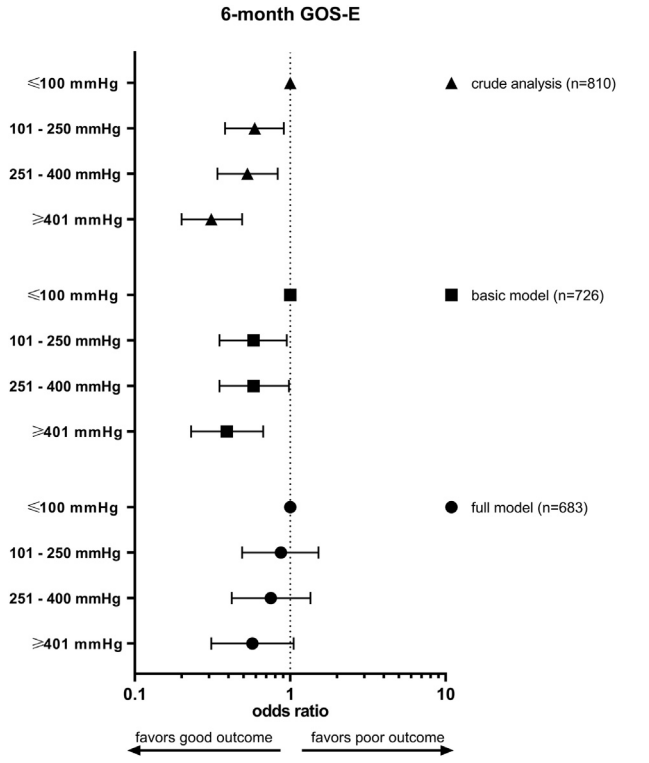

Figure 1. Forest plot presenting the association between different early oxygenation levels and 6-month neurologic status. Neurologic status, assessed by the GOS-E, was dichotomized into good outcome (namely, moderate disability or good recovery; GOS-E >4) versus poor outcome (namely, death, or vegetative state, or severe disability; GOS-E ≤4). Early oxygenation levels were assessed by the worst value of arterial partial pressure of oxygen (PaO_2) during the first 4 hours of presentation in the emergency department. A PaO_2 of ≤100 mmHg was utilized as a "reference" category to calculate ORs with 95% confidence intervals on binary logistic regression. The "crude (unadjusted)" model involves PaO_2. The "basic" model involves PaO_2, age, pupillary reactivity, and Revised Trauma Score. The "full" model includes variables of the basic model, plus admission hemoglobin, and Marshall CT classification score and Injury Severity Score.

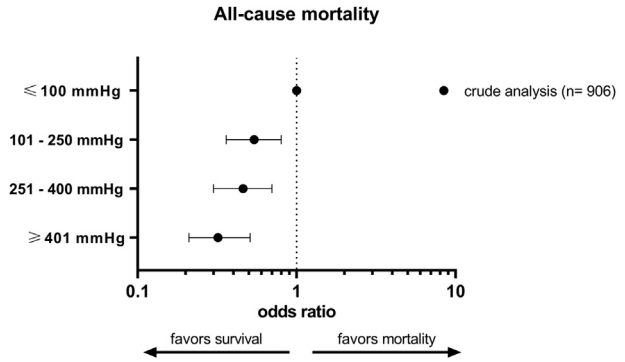

Figure 2. Forest plot presenting the association between different early oxygenation levels and all-cause mortality. Mortality was assessed within 28 days from trial enrollment. Early oxygenation levels were assessed by the worst value of arterial partial pressure of oxygen (PaO_2) during the first 4 hours of presentation in the emergency department. A PaO_2 of ≤100 mmHg was utilized as a "reference" category to calculate ORs with 95% confidence intervals on binary logistic regression.

within 24 hours from hospital admission were associated with the worse long-term neurologic status of patients with traumatic brain injury. To explain this seeming contradiction, one could point out that the former studies (namely, ours and that by Fujita et al[25]) considered oxygenation levels as early as 4 to 6 hours from presentation in the emergency department, whereas the latter 2 studies (namely, by Brenner et al[26] and by Alali et al[27]) considered oxygenation levels at a later phase (ie, within 24 hours from hospital admission). Taken together, one could infer that high oxygenation levels may not be harmful during the first hours of traumatic brain injury when brain metabolism is acutely altered[28,29]; whereas, at a later phase (in the intensive care unit setting), a U-shaped association between oxygenation levels and clinical outcomes might exist, potentially supporting a conservative approach regarding oxygenation levels.[30,31] Briefly, optimal oxygenation levels may depend on the time from the onset of traumatic brain injury.

Regarding our secondary outcomes, we found that higher systemic oxygenation (even $PaO_2 \geq 401$ mmHg) was less likely to be associated with the development of acute respiratory distress syndrome than PaO_2 of ≤100 mmHg. This finding may seem counterintuitive as hyperoxia might precipitate lung injury.[14,32] Therefore, one could argue that this finding may simply reflect worse trauma-related lung injury (such as contusions) or the higher likelihood of the presence of confounders (such as aspiration and difficult intubation) in the group of PaO_2 of ≤100 mmHg than $PaO_2 \geq 401$ mmHg.

In conclusion, the present secondary analysis of data from 910 patients enrolled in a large Resuscitation Outcomes Consortium randomized controlled trial suggests that high oxygenation levels as early as the first 4 hours of presentation in the emergency department may not be adversely associated with the long-term neurologic status of patients with severe traumatic brain injury. Given that the early phase of traumatic brain injury is critical,[33] during that phase, clinicians may focus on stabilizing patients while giving low priority to titration of oxygenation levels.

This study was prepared using research materials from the Traumatic Brain Injury Hypertonic Saline randomized controlled trial conducted by the Resuscitation Outcomes Consortium. The research materials were obtained from the Biologic Specimen and Data Repository Information

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