PAPER

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Association Between Early Hyperoxia and Worse Outcomes After Traumatic Brain Injury

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Objective: To investigate the relationship between oxygenation and short-term outcomes in patients with traumatic brain injury (TBI).

Design: Logistic regression analysis was used to determine whether average high (>200 mm Hg) or low (<100 mm Hg) Pa_{O_2} levels within the first 24 hours of hospital admission correlated with patient outcomes relative to patients with average Pa_{O_2} levels between 100 and 200 mm Hg.

Setting: Level 1 trauma center.

Patients: We retrospectively reviewed 1547 consecutive patients with severe TBI who survived past 12 hours after hospital admission.

Main Outcome Measures: We measured mortality, intensive care unit length of stay, hospital length of stay, and discharge Glasgow Coma Scale (GCS) score.

Results: Of the 1547 patients, 77% were male and 89% sustained blunt trauma. Mean (SD) age, admission GCS score, and Injury Severity Score were 41.3 (20.6) years, 8.3 (4.7), and 31.9 (12.5), respectively. Mean (SD) intensive care unit length of stay and hospital length of stay were 8.7 (10.5) days and 13.8 (13.7) days, respectively. Mean (SD) discharge GCS score was 10.1 (4.7). The mortality rate was 28%. After controlling for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score, patients with high Pa_{O_2} levels had significantly higher mortality and lower discharge GCS scores than patients with a normal Pa_{O_2} ($P<.05$). Patients with low Pa_{O_2} levels also had increased mortality ($P<.05$).

Conclusions: Hyperoxia within the first 24 hours of hospitalization is associated with worse short-term functional outcomes and higher mortality after TBI. Although the mechanism for this has not been completely elucidated, it may involve hyperoxia-induced oxygen-free radical toxicity with or without vasoconstriction. Hyperoxia and hypoxia were found to be equally detrimental to short-term outcomes in patients with TBI. A narrower therapeutic window for oxygenation may improve mortality and functional outcomes.

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HYPOXIA HAS BEEN DOCUMENTED to significantly worsen outcomes in patients with traumatic brain injury (TBI).[1-5] The Guidelines for the Management of Severe Traumatic Brain Injury published in 2007 by the Brain Trauma Foundation outlined evidenced-based recommendations for oxygen therapy. Owing to the lack of strong evidence, the summary only suggests that hypoxia (Pa_{O_2} < 60 mm Hg) be avoided.[6]

While it is clear that hypoxia is detrimental, little is known about the effects of other oxygen levels. Some studies have reported worsened physiologic parameters with hyperoxia.[7] Others have found improved parameters,[8,9] while still others have reported no benefit.[10] Most studies have investigated the effects of oxygen levels on cerebral metabolic rate, cerebral blood flow, lactate to pyruvate ratios, brain tissue oxygenation, cerebral arteriovenous oxygen tension difference, and/or jugular bulb venous oxygen tension.[10-13] To our knowledge, few studies have examined the effects on patient outcomes. We investigated the relationship between hypo-oxygenation and hyperoxygenation and short-term outcomes in patients with TBI.

See Invited Critique at end of article

METHODS

We retrospectively reviewed consecutive patients with severe TBI (sTBI) who survived more than 12 hours after admission between June 2002 and June 2007. Severe TBI patients were defined as patients with a head Abbreviated Injury Score of 3 or greater.

We collected data on mortality, intensive care unit length of stay (ICULOS), hospital length of stay (HLOS), and discharge Glasgow Coma Scale (GCS) score. Logistic regression analysis was used to compare average high (>200 mm Hg, hyperoxic), normal (100-200 mm Hg, normoxic), and low (<100 mm Hg, hypoxic) Pao_2 levels within the first 24 hours of hospital admission with regard to short-term patient outcomes. The Pao_2 values were obtained from arterial blood gas measurements a mean (SD) of 4.3 (3) times per patient during the first 24 hours of hospital admission. Those values were averaged to give the final Pao_2 determination for subgroup analysis. Further analyses included unadjusted and adjusted pairwise comparisons among the 3 Pao_2 level categories. Subject age, sex, Injury Severity Score, mechanism of injury, and admission GCS score were controlled for in the adjusted models. The cutoff points for Pao_2 levels were chosen by combining 2 factors: hemoglobin is 100% saturated at Pao_2 levels of around 80 mm Hg, and the lowest normal Pao_2 level in our laboratory is 100 mm Hg. Mortality rates were defined by in-hospital death from any cause. Short-term functional outcomes were measured by GCS scores on hospital discharge. Poor short-term outcome was defined by a discharge GCS score of between 3 and 8, while a good outcome was indicated by a discharge GCS score of 9 or greater. Length of hospital stay was analyzed after stratification into groups of patients who spent less than 7 days vs greater than or equal to 7 days in the hospital or ICU.

The study was approved by the institutional review board at the University of Maryland School of Medicine.

RESULTS

A total of 1547 patients were included in the analysis. Seventy-seven percent were male, and 89% sustained blunt trauma. Mean (SD) age, admission GCS, and Injury Severity Score were 41.3 (20.6) years, 8.3 (4.7), and 31.9 (12.5), respectively. Mean (SD) ICULOS and HLOS were 8.7 (10.5) days and 13.8 (13.7) days, respectively. Average (SD) discharge GCS score was 10.1 (4.7) (**Table 1**). The mean total in-hospital mortality rate was 28% across all 3 Pao_2 groups. Mortality by group is listed in **Table 2**.

Initial comparison of the 3 Pao_2 levels indicated that statistically significant differences existed between hypoxic, normoxic, and hyperoxic patients with regard to mortality, discharge GCS score, HLOS, and ICULOS. Pairwise comparisons were then examined to determine where specific differences occurred. After controlling for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score, patients with average Pao_2 levels less than 100 mm Hg had significantly higher mortality and worse discharge GCS scores compared with normoxic patients (**Table 3**). Hypoxic patients also had a shorter HLOS and ICULOS compared with normoxic patients (Table 3).

Hyperoxic patients were also found to have significantly worse short-term outcomes compared with normoxic patients (**Table 4**). There was no difference in ICULOS between hyperoxic and normoxic patients. To further control for patient injury severity, a logistic regression model controlling for admission systolic blood pressure was performed. The results mirrored our original regression model. Mortality (odds ratio, 1.56; 95% CI, 1.18-2.07; $P=.002$), discharge GCS score (odds ratio, 1.56; 95% CI, 1.2-2.04; $P=.001$), and HLOS (odds ratio, 0.74; 95% CI, 0.58-1.13; $P=.01$) was significantly worse for hyperoxic patients compared with normoxic patients, while ICULOS was not significant.

A comparison of mortality between hyperoxia and hypoxia indicated no statistical difference between the groups (31.1% vs 37.9%; $P=.17$) (**Table 5**). No differences in short-term functional outcome were found between the 2 adjusted groups. However, there was a difference in HLOS and ICULOS favoring the hyperoxic group, which was more likely than the hypoxic group to have hospital

Table 1. Patient Demographics

Characteristic (N=1547)	Mean (SD)
Age, y	41.3 (20.6)
Hospital length of stay, d	13.8 (13.7)
ICU length of stay, d	8.7 (10.5)
Discharge GCS score	10.1 (4.7)
ISS	31.9 (12.5)
Admission GCS score	8.3 (4.7)
Method of injury, %	
Blunt	89
Penetrating	10
Other	1
Sex, %	
Male	77
Female	23

Abbreviations: GCS, Glasgow Coma Scale; ICU, intensive care unit; ISS, Injury Severity Score.

Table 2. Mortality Within Groups by Average Pao_2 Values in the First 24 Hours of Hospital Admission

Average Pao_2 Level Within 24 h, mm Hg	No. (%)		% Total Deaths (n=437)
	Total (n=1547)	Deaths, Total/group	
<100	103 (7)	39 (38)	9
100-200	778 (50)	191 (25)	44
>200	666 (43)	207 (31)	47

Table 3. Effect of Hypoxia Compared With Normoxia on Outcome Measures[a]

	OR (95% CI)	*P* Value
<100 vs 100-200 mm Hg		
Mortality	2.20 (1.33-3.63)	.002[b]
Discharge GCS score 3-8	1.66 (1.01-2.75)	.05[b]
HLOS	0.38 (0.25-0.58)	<.001[b]
ICULOS	0.40 (0.25-0.66)	<.001[b]

Abbreviations: GCS, Glasgow Coma Scale; HLOS, hospital length of stay; ICULOS, intensive care unit length of stay; OR, odds ratio.

[a] Adjusted for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score.

[b] $P<.05$.

Table 4. Effect of Hyperoxia Compared With Normoxia on Outcome Measures[a]

	OR (95% CI)	*P* Value
>200 vs 100-200 mm Hg		
Mortality	1.50 (1.15-1.97)	.003[b]
Discharge GCS score 3-8	1.52 (1.18-1.96)	.001[b]
HLOS	0.75 (0.60-0.94)	.01[b]
ICULOS	0.92 (0.74-1.15)	.46

Abbreviations: GCS, Glasgow Coma Scale; HLOS, hospital length of stay; ICULOS, intensive care unit length of stay; OR, odds ratio.
[a] Adjusted for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score.
[b] $P<.05$.

Table 5. Effect of Hyperoxia Compared With Hypoxia on Outcome Measures[a]

	OR (95% CI)	*P* Value
>200 vs <100 mm Hg		
Mortality	0.59 (0.35-1.00)	.05
Discharge GCS score 3-8	0.81 (0.48-1.37)	.44
HLOS	1.90 (1.22-2.96)	.005[b]
ICULOS	2.26 (1.38-3.70)	.001[b]

Abbreviations: GCS, Glasgow Coma Scale; HLOS, hospital length of stay; ICULOS, intensive care unit length of stay; OR, odds ratio.
[a] Adjusted for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score.
[b] $P<.05$.

and ICU durations of 7 or more days. Further analysis of mortality as a function of hospital stay and average Pa_{O_2} levels demonstrated that 90% of hypoxic patients who died did so in less than 7 days compared with 76% of hyperoxic patients (**Table 6**).

Table 6. Mortality Within Groups by Average Pa_{O_2} Values

	No. (%)			*P* Value
	<100 mm Hg	100-200 mm Hg	>200 mm Hg	<100 vs >200 mm Hg
Deaths, No.	39	191	207	
Deaths within 7 d	35 (90)	142 (74)	157 (76)	.05

COMMENT

The relationship between hypoxia and TBI has been thoroughly evaluated during the past few decades. Several studies have reported poor outcomes and/or worsening physiologic parameters with hypoxia, which has led the Brain Trauma Foundation to recommend avoiding Pa_{O_2} levels below 60 mm Hg in patients with TBI. The guidelines outline a key point in the care of patients with TBI, which formed the basis of a portion of our study—that the levels of hypoxia that correlate to poor outcomes are unknown. In addition, treatment strategies and optimal resuscitation protocols are yet to be determined.

The conclusion that hypoxia is detrimental to the injured brain is reinforced by our data. Results from other studies are derived from a variety of methods. Some used the absolute number of hypoxic episodes,[5] while others measured brain tissue oxygen tension levels[14] or other cerebral physiologic parameters.[15] Mortality and short-term functional outcome were significantly poorer with Pa_{O_2} levels less than 100 mm Hg. Our definition of hypoxia correlates with a recent study by Davis et al[3] that reported a clear survival advantage to patients with TBI with arrival Pa_{O_2} levels greater than 110 mm Hg. Combining the 2 studies yields convincing evidence from more than 4900 patients with TBI that targeting Pa_{O_2} levels greater than 100 to 110 mm Hg is most beneficial to the brain-injured patient, at least within the first 24 hours.

Owing to the evidence that hypoxia is clearly detrimental to patients with TBI, recent research has focused on hyperoxia. The methods used to investigate hyperoxia have varied, but most have revolved around the administration of high levels of fraction of inspired oxygen (F_{IO_2}) for specific periods of time and subsequent measuring of both direct and indirect levels of cerebral metabolites.[8,10,16] The studies have been inconclusive largely owing to our inability to completely understand the brain's extensive metabolism, and the fact that simply increasing the percentage of inspired oxygen may not reflect any changes in cerebral metabolism as a result. Even more complex is the translation of these findings to usable outcome measures.

To our knowledge, only 2 studies in the literature have documented the relationship between hyperoxia and functional outcomes. Tolias et al[8] found that while some metabolic parameters changed with administration of 100% F_{IO_2} to patients with sTBI, no difference in 6-month Glasgow Outcome Scale scores was observed. It is difficult to compare this study with our data owing to the fact that the patients received 24 hours of hyperoxia, without Pa_{O_2} correlation. Davis et al[3] reported poor functional outcomes in patients with TBI with admission Pa_{O_2} levels greater than 487 mm Hg. The liberal definition of good outcome used in their investigation also makes this a difficult comparison to our data, which are based on GCS scores. However, it does suggest the importance of defining hyperoxia, which differs between our studies. Davis et al used logistic regression models to determine the limit below which oxygenation causes no harm (487 mm Hg), while we chose our upper limit of 200 mm Hg based purely on clinical parameters. We routinely observe Pa_{O_2} levels between 100 and 200 mm Hg, while rarely seeing values greater than 200 mm Hg, at least for long periods. Our data suggest that an even narrower therapeutic window exists for improved outcomes in patients with TBI. The high upper limit of normoxia in the Davis et al study may be partially due to the fact that their data were derived from arrival Pa_{O_2} only, and many patients in the field are pre-oxygenated with 100% F_{IO_2}. It is possible that initial or arrival Pa_{O_2} levels between 200 and 487 mm Hg are not harmful as long as they are decreased rapidly to lower levels. As we only obtained average levels, it is difficult to predict the hourly change in Pa_{O_2} levels and their final consequences.

An additional finding unique to our study is that hyperoxia is just as detrimental to the mortality and short-term functional outcome of patients with sTBI as hypoxia. This highlights the critical importance of finding a therapeutic window for targeting Pa_{O_2} in the first 24 hours of hospitalization, which we believe to be between 100 and 200 mm Hg. The additional length of ICU and hospital stay in hyperoxic patients may be explained by the greater proportion of hypoxic deaths that occurred within 7 days (Table 6), while similar proportions of hyperoxic and normoxic deaths occurred within the same period.

There is enough evidence to caution the use of hyperoxia in patients with sTBI, although the mechanisms by which this occurs is unknown. Ventilation with high oxygen levels has been associated with injury to many cell types, including brain, lung, heart, and eyes.[17] The damage has been attributed to the formation of free radicals. Unfortunately, to our knowledge, only a few studies in animal models have been able to measure an increase in reactive oxygen species,[18,19] while studies in humans have not been able to show any correlation between hyperoxia and oxygen toxicity.[13,20] It is well-known that 100% oxygen can cause cerebral vasoconstriction, but several studies suggest that the increase in oxygen delivery more than compensates for the vasoconstriction, at least on a cellular level. Thus, it is unknown whether, directly or indirectly, the outcomes are a result of vasoconstriction, free radical toxicity, changes in cerebral metabolism or intracranial pressure, or a combination of these factors.

As this was a retrospective database study, several limitations exist. First, our definition of hyperoxia was determined from approximately 4.3 Pa_{O_2} values for each patient during a 24-hour period, which may not accurately reflect the Pa_{O_2} levels per minute or hour. Second, we are unable to determine the patients' locations in the hospitals for all periods in the first 24 hours, which may have resulted in higher levels of oxygen being administered. Unfortunately, we are unable to explain a direct cause for the poor outcome of hyperoxia patients with sTBI, and more studies must be performed in an attempt to link the metabolic changes to outcome measures. In addition, further investigation into the specific type of traumatic brain injury, as well as other specific types of injury (such as thoracic injury), is likely to be helpful in understanding these results.

Hyperoxia within the first 24 hours of hospitalization worsens short-term functional outcomes and increases mortality after TBI. While unclear, the mechanism may involve hyperoxia-induced oxygen-free radical toxicity, with or without vasoconstriction. Hyperoxia and hypoxia were found to be equally detrimental to short-term outcomes in patients with TBI. A narrower therapeutic window for oxygenation may improve mortality and functional outcomes.

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Hyperoxia and Traumatic Brain Injury

Brenner and colleagues[1] have nicely shown that average PaO_2 levels of less than 100 mm Hg or greater than 200 mm Hg are independently associated with higher mortality and worse discharge Glasgow Coma Scale scores in 1547 patients with a brain Abbreviated Injury Score of 3 or greater after risk adjusting for mechanism of injury, age, Injury Severity Score, sex, and admission Glasgow Coma Scale score. It has been well established that hypoxia is detrimental to outcome in brain injury. Because of this, there may be a tendency to give higher levels of oxygen to prevent hypoxia. Indeed, the authors found that 43% of their patients had PaO_2 values greater than 200 mm Hg in the first 24 hours of care. Unfortunately, this hyperoxia appears to be detrimental to outcome compared with normoxia and is just as bad as hypoxia. If true, these are important findings that could change the way we approach patients with traumatic brain injury.

There are a number of questions raised by the study that must be answered before this truth can be established. First, why was there variability in PaO_2 values? Second, the mean Injury Severity Score of patients in the study was 31.9, so many of these patients must have had multiple-system injuries. These other severe injuries and a marker of hemorrhagic shock such as admission hypotension or 24-hour blood transfusion were not included in the risk adjustment model. It would also be important to know whether hyperoxia was an independent predictor of death from brain injury rather than death from other injuries. Finally, hyperoxia is known to decrease regional cerebral blood flow by vasoconstriction as a result of the decreased carbon dioxide–carrying capacity of super-oxygenated hemoglobin, the so-called Haldane effect. Additionally, patients with the most severe brain injuries might also be treated with hyperventilation, which may be related to increased levels of PaO_2 and may also be a risk factor for outcome. Therefore, it would also be important to look at $PaCO_2$ values both in relation to PaO_2 values and outcome. In short, I believe this article raises the important possibility that overshooting normal PaO_2 values in an attempt to prevent hypoxia in patients with traumatic brain injury may be detrimental. Further work to establish this relationship as independent from other important risk factors in this complicated group of patients is indicated.

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