Annals of Trauma & Acute Care

Research Article
Published: 19 Mar, 2021

The Effect of Hyperoxia in Traumatic Brain Injury Patients in the Intensive Care Unit of a Tertiary Care Center

*Sarah Alromaih[1], Hind Alshabanat[1], Nosaiba Alshanqiti[1], Almaha Aldhuwaihy[1], Sarah Abdullah Almohanna[1], Muna Alqasem[1], Fatmah Othman[1,2] and Raymond M Khan[1]**

[1]*Trauma & Intensive Care Unit, Collage of Medicine King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia*

[2]*Department of Research, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia*

Abstract

Background: Traumatic Brain Injury (TBI) is a leading cause of morbidity and mortality globally. Currently, the association between hyperoxia and outcomes in patients with TBI remains debatable. We assessed the effect of hyperoxia on the neurological outcomes and survival of critically ill patients with moderate-severe TBI.

Methods: This was a retrospective cohort study of all adults with moderate-severe TBI admitted to the ICU between January 1st, 2016 and December 31st, 2019 who required invasive mechanical ventilation. We noted ABGs performed with the first 3 h of intubation, then 6 h to 12 h and 24 h to 48 h. The patients were divided into two categories: Normoxia (PaO_2 60 mmHg to 99 mmHg) and hyperoxia (PaO_2>100 mmHg). Multivariable logistic regression was performed to assess predictors of hospital mortality and good neurologic outcome (Glasgow outcome score [GOS] ≥ 4). In a second analysis the patients were divided into survivors and non-survivors.

Results: The study included 308 patients: 23.4% (n=72) in normoxia group and 76.6% (n=236) in hyperoxia group. Hyperoxia was not associated with increased hospital (43% *vs.* 18%, p=0.20) mortality. Further, the hospital discharge GCS (10 ± 5 *vs.* 11 ± 4, p=0.10) and GOS (3 ± 1 *vs.* 3 ± 1, p=0.35) were similar. In multivariable logistic regression analysis, hyperoxia was not associated with increased mortality (adjusted Odds Ratio [aOR] 0.99, 95% CI 0.99 to 1.00, p=0.11). PaO_2 within different ranges was also not associated with mortality: 100 mmHg to 200 mmHg: aOR=0.60, 95% CI 0.29 to 1.52; 201 mmHg to 300 mmHg: aOR=0.66, 95% CI 0.29 to 1.52; 301 mmHg to 400 mmHg: aOR=0.80, 95% CI 0.31 to 2.09; and >400 mmHg: aOR=0.39, 95% CI 0.14 to 1.08; reference: PaO_2 60 mmHg to 99 mmHg. The Kaplan-Meier survival curve for normoxia verses hyperoxia showed no significant difference for all-cause mortality. In the survivors verse non-survivors analysis, the PaO_2 were (median, IQT) 199 mmHg (111 to 329) and 165 mmHg (84 to 252), respectively.

Conclusion: Hyperoxia (PaO_2>100 mmHg) was not associated with increased mortality or poor neurological outcomes (determined by GOS) in moderate-severe TBI patients.

Keywords: Hyperoxia; Traumatic brain injury; Mortality; Neurological outcomes; Intensive care; Mechanical ventilator

OPEN ACCESS

Correspondence:
Raymond M Khan, Department of Intensive Care, College of Medicine King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdul-Aziz Medical City, P.O. Box: 22490, Mail Code 1425, Riyadh, Saudi Arabia,
E-mail: raymondkhan@yahoo.com

Received Date: *16 Feb 2021*
Accepted Date: *16 Mar 2021*
Published Date: *19 Mar 2021*

Citation:
Alromaih S, Alshabanat H, Alshanqiti N, Aldhuwaihy A, Almohanna SA, Alqasem M, et al. The Effect of Hyperoxia in Traumatic Brain Injury Patients in the Intensive Care Unit of a Tertiary Care Center. Ann Trauma Acute Care. 2021; 5(1): 1023.

Introduction

Traumatic Brain Injury (TBI) is a major cause of death, morbidity and economic burden globally, with more than 13 million people estimated to live with disabilities related to TBI in Europe and USA [1]. However, the magnitude of this problem may be even greater than envisioned, as a significant number of patients survive hospitalization but ultimately succumb to complications of their injuries [2]. Thus, clear individualized approach considering the pathophysiological diversity of TBI is of vital importance.

The primary injury in TBI cannot be reversed; hence, current management strategies and research are focused on preventing secondary insults by avoiding hypotension and hypoxia, thus maintaining appropriate cerebral blood flow and oxygen delivery [3]. Immediately following TBI, the metabolic demand of the brain increases, but oxygen delivery may decrease due to a reduction of CBF, increased ICP, and decreased oxygen diffusion caused by capillary endothelium edema, secondary to the neuroinflammatory response [4]. This oxygen deficiency forces conversion to

anaerobic metabolism, leading to depletion of cellular ATP, calcium influx, release of excitatory neurotransmitters and mediators of programmed cell death [5]. Hyperoxia in acute brain injury reverses the anaerobic state, with increased brain tissue PaO_2, reduced lactate pyruvate ratio, increased cytochrome C oxidase and cerebral metabolic rates [6]. Thus, there is a paradigm shift in some clinicians to accept hyperoxia (PaO_2>100 mmHg or 13.3 kPa) in order to improve oxygen delivery [7]. However, oxygen resuscitation frequently exceeds physiological requirement and toxicity may ensue as elevated PaO_2 induces vasoconstriction and reduces cardiac output, which may impair blood flow, paradoxically lowering the delivery of oxygen [8]. Also, exposure to high fractions of inspired oxygen may amplify the production of oxygen free radicals, resulting in neuronal injury *via* calcium influx causing excitotoxic damage or oxidative damage to the electron transport chain leading to decrease ATP production and subsequent activation of apoptotic pathways [9-11].

The clinical relationship between hyperoxia and outcome in patients with TBI remains controversial, with published studies having mixed results and thus there is no consensus on the ideal PaO_2 target in TBI. A retrospective study in patients with severe TBI showed that hyperoxia (PaO_2>487 mmHg/64.9 kPa) was associated with decreased survival (OR: 0.50, 95% CI 0.36 to 0.71; p<0.001) [12]. Similar findings were obtained in a multicenter study among mechanically ventilated patients suffering from TBI, where hyperoxia (PaO_2>300 mmHg) within 24 h after admission was independently associated with higher in-hospital mortality (OR: 1.5, 95% CI 1.02 to 2.4; p=0.04) [13]. Brenner and associates, in a logistic regression model showed that mortality (OR: 1.56; 95% CI 1.18 to 2.07; p=0.002) and hospital length of stay (OR: 0.74; 95% CI 0.58 to 1.13; p=0.01) were significantly worse for hyperoxic (PaO_2>200 mmHg/26.7 kPa) patients [14]. On the other hand, Raj and associates found in patients with moderate-to-severe TBI that hyperoxia (PaO_2>100 mmHg/13.3 kPa) was not predictive of 6 month mortality [15]. Russell et al. [2] observed among their patients with TBI that PaO_2 was not related to increased mortality (OR: 1.27, 95% CI 0.72 to 2.25). Likewise, Fujita and colleagues, found that PaO_2 was significantly greater in patients with favorable outcomes than in patients with unfavorable neurological outcomes (PaO_2: 252 ± 122 *vs.* 202 ± 87 mm Hg, p=0.008), and PaO_2 was independently associated with survival following severe TBI [16]. Finally, in a large multicenter cohort of TBI patients, hyperoxia in the first 24 h after ICU admission was not independently associated with greater in-hospital mortality [17].

This disparity in findings is witnessed in two meta-analyses using the same studies, but yielding different conclusions. Damiani et al. [18] claims that hyperoxia may be associated with increased mortality in patients with TBI, while Helmerhorst et al. [19] found that hyperoxia was not independently associated with increased mortality. In a more recent meta-analysis, Ni et al. showed that hyperoxia was not associated with worse mortality in TBI patients.

Significant clinical ambiguity still exists in regard to the benefit or harm of hyperoxia in TBI patients. This uncertainty paired with the immense burden of TBI in the Kingdom of Saudi Arabia and lack of data in our patient population has led us to perform a retrospective cohort study to investigate if hyperoxia in the first 24 h of admission would affect the outcomes of moderate-severe TBI patients. We believe that this data could yield vital information needed to optimally manage our patients and it may add some clarity to the haziness encircling hyperoxia that still exists today.

Methods

Parents and setting

This was a retrospective cohort study of all consecutive adult patients with moderate-sever TBI who were admitted to the Intensive Care Unit (ICU) at King Abdulaziz Medical City, a 1000 bed tertiary care center in Riyadh, Saudi Arabia. The critical care units were covered by board-certified intensivists with onsite coverage 24 h/day and a nurse-to-patient ratio of 1:1. The hospital was accredited by joint commission international and had active trauma and neurosurgical teams. We included all adult patients (>18 years) admitted to ICU after TBI and a GCS ≤ 12, from January 1st, 2016 to December 31st, 2019. Patients were all intubated, on a mechanical ventilator with Arterial Blood Gas (ABG) done within 20 min of being intubated and, repeated 3 to 6, 12 to 24, and 48 h after intubation. We excluded patients who were admitted in ICUs for less than 72 h, those with labeled no code, comfort care, supportive care or brain dead, or with incomplete medical records. The Institutional Review Board and of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, approved this study and waived the requirement for informed consent (RYD-19-419812-59135).

Data collection

A list was generated of all patients admitted to the ICU that fulfill the inclusion criteria. Data were obtained from the computer chart for the analysis. These data included demographic characteristics, source of ICU admission, the severity of illness on ICU admission assessed by Injury Severity Score (ISS), Revised Trauma Score (RTS), Shock Index (SI), and The International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) in TBI core model (using age, motor function and pupil response), admission and discharge Glasgow Coma Score (GCS), laboratory parameters, ABGs results, Computerized Tomography (CT) findings, and the therapeutic intervention. The PaO_2 on intubation and within 3 to 6, 12 to 24, and 48 h, the corresponding Fraction of Inspired Oxygen (FiO2), and Positive End Expiratory Pressures (PEEP) were documented. For the PaO_2 level, patients were categorized into normoxia (PaO_2 60 mmHg to 99 mmHg) and hyperoxia (PaO_2>100 mmHg) groups depending on their ABG findings within 3 h of intubation. Data on study outcomes were collected for each patient that includes: ICU and hospital mortality, hospital length of stay (measured in days), tracheostomy, and. Glasgow Outcome Score (GOS) at hospital discharge day.

Study design

In this study, we analyzed the data in two different approaches. In the first analysis, patients were categorized into in normoxia (PaO_2 60 mmHg to 99 mmHg) and hyperoxia (PaO_2>100 mmHg) groups depending on their Arterial Blood Gas (ABG) findings within 3 h of intubation. We examined for predictors of outcome (mortality and neurological status). We also examined if hyperoxia may have an effect on subgroups and if different ranges of PaO_2 (PaO_2: 50 mmHg to 99 mmHg, 100 mmHg to 200 mmHg, 201 mmHg to 300 mmHg, 301 mmHg to 400 mmHg and >400 mmHg) may influence outcomes. In the second analysis, the patients were divided into survivors and non-survivors depending on their mortality outcome, and their characteristics were examined.

Statistical analysis

The patient's demographic and clinical data were presented as means (Standard Deviations: SD) for the continuous variables if

Table 1: Baseline characteristics of normoxia (PaO_2 60 mmHg to 100 mmHg) and hyperoxia (PaO_2>100 mmHg).

Variables	All (n=308)	Normoxia (n=72)	Hyperoxia (n=236)	P value
Age (years), median (IQR)	28 (23-36)	30 (11)	31 (12)	0.59
Male Gender, N (%)	292 (94.8)	70 ± 97	222 ± 94	0.37
Weight, kg (mean ± SD)	68 ± 16	70 (17)	67 ± 14	0.1
IDBW, kg (mean ± SD)	65 ± 6	64 ± 6	65 ± 6	0.7
Markers of severity, (mean ± SD)				
Injury severity score	29 ± 7	31 ± 7	29 ± 7	0.11
Revised trauma score	5.3 ± 1	5.3 ± 1	5.3 ± 1	0.93
Shock index	0.86 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.32
IMPACT mortality	27.9 ± 18	29 ± 18	27 ± 17	0.47
Vital signs at admission, (mean ± SD)				
MAP, mmHg	94 ± 22	91 ± 23	95 ± 22	0.18
Heart rate, beats/min	104 ± 28	108 ± 29	103 ± 27	0.19
Respiratory rate, breaths/min	24 ± 7	24 ± 7	24 ± 6	0.73
Oxygen saturation, %	95 ± 8	92 ± 13	96 ± 6	0.002
Temperature, °C	36.6 ± 0.6	36 ± 0.7	36.7 ± 0.6	0.3
CVP, mmHg	10.6 ± 4.5	12 ± 5	10 ± 4	0.012
Arrival GCS, N (%)				
GCS 9-12	56 (18.1)	61 (84)	191 (80)	0.46
GCS ≤ 8	252 (81.8)	11 (15)	45 (19)	
Laboratory parameters, (mean ± SD)				
Hemoglobin, gm/L	138 ± 24	138 ± 26	138 ± 24	0.92
Platelets, 109/L	271 ± 90	266 ± 104	273 ± 86	0.58
Sodium, mmol/L	139 ± 4	140 ± 4	139 ± 4	0.17
Creatinine, umol/L(median, IQR)	81 (71-96)	84(73-104)	80 (70-95)	0.006
Lactic acid, mmol/L(median, IQR)	2.4 (1.4-3.9)	3 (1.9-4.2)	2.2 (1.3-3.7)	0.32
AST, U/l (median, IQR)	62 (36-122)	93 (59-149)	55 (34-103)	0.023
ALT,U/L(median, IQR)	43 (25-84)	72 (40-118)	37 (24-79)	0.02
Respiratory and ventilator parameters, (mean ± SD)				
Tidal volume per IDBW, mL/kg	6.5 ± 0.7	6.6 ± 0.6	6.5 ± 0.8	0.22
FiO_2, %	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.26
pH	7.2 ± 0.08	7.2 ± 0.09	7.3 ± 0.08	0.002
$PaCO_2$, mmHg	43 ± 9	44 ± 10	42 ± 8	0.08
PaO_2, mmHg (median, IQR)	194 (105-308)	81 (71-92)	246 (162-357)	<0.001
PaO_2/FiO_2 ratio, (median, IQR)	267 (147-433)	91 (78-141)	343 (216-466)	<0.001
CT head findings, N (%)				
Isolated head injury	96 (31.1)	13 (18)	83 (35)	0.006
Epidural hematoma	26 (8.4)	7 (9)	19 (8)	0.78
Subdural hematoma	125 (40)	27 (37)	98 (41)	0.54
Subarachnoid hemorrhage	115 (37.3)	27 (37)	88 (37)	0.97
Intraparenchymal hemorrhage/contusion	151 (49)	34 (47)	38 (52)	0.72
Intraventricular hemorrhage	46 (14.9)	12 (16)	34 (14)	0.63
Cerebral edema	106 (34)	26 (36)	80 (33)	0.72
Midline Shift ≥ 5 mm	42 (13.6)	9 (12)	33 (13)	0.74
No bleeding on CT	50 (16)	11 (15)	39 (16)	0.8
Management, N (%)				
Blood product transfusions				
PRBC	114 (37)	34 (47)	81 (34)	0.04

Fresh Frozen Plasma	66 (82)	18 (90)	48 (80)	0.31
Platelets	49 (79)	13 (86)	36 (76)	0.4
Tranexamic acid, N (%)	95 (30)	26 (36)	70 (29)	0.62
ICP Monitoring, N (%)	54 (15)	14 (19)	39 (15)	0.76
Hypertonic saline, N (%)	174 (55)	57 (52)	134 (56)	0.57
Head injury protocol, N (%)	225 (72)	52 (72)	173 (72)	0.96

SD: Standard Deviation; IMPACT: International Mission for Prognosis and Analysis of Clinical Trials; MAP: Mean Arterial Pressure; CVP: Central Venous Pressure; GCS: Glasgow Come Scale; AST: Aspartate Transaminase; ALT: Alanine Transaminase; IDBW: Ideal Body Weight; FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End-Expiratory Pressure; $PaCO_2$: Partial Pressure of Carbon Dioxide; PaO_2: Partial Pressure of Oxygen; PaO_2/FiO_2: Ratio of Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen; ICP: Intracranial Pressure

normally distributed, otherwise median and Interquartile Range (IQR) were used, where the categorical variables were presented as frequencies and percentages. We compared the baseline characteristics between normoxia and hyperoxia patients using Chi-squared (or Fisher's exact test if indicated), and Student t-test or ANOVA for continuous variables. In the multivariable logistic regression analysis for the predictors of hospital mortality and neurologic outcome (GOS ≥ *vs.* <4), the following variables were entered in the model: Age, Injury Severity Score (ISS), arrival Glasgow Coma Scale (GCS), systolic blood pressure >90 mmHg and the presence of midline shift >5 mm on brain CT. The results were presented as an Odds Ratio (OR) with a 95% confidence interval (95% CI) with a p-value <0.05 was considered statistically significant.

A Kaplan-Meier survival curve was carried out to demonstrate the probability of survival overtime for hyperoxia and normoxia patients. All analyses were done with the Stata 12 software system (Stata Corp L.P., College Station, TX).

Results

The baseline characteristics of the cohort are presented in Table 1. The patient's were predominately young males, with a vast majority being admitted from the emergency department. There were some significant differences between the normoxia and hyperoxia groups. Hyperoxic patients had significantly lower central venous pressure, creatinine, positive end-expiratory pressure, partial pressure of carbon dioxide and RBC transfusions, but higher rates of isolated head injury.

Table 2 describes the clinical outcome of our cohort. Hyperoxia was not associated with a prolonged ICU or hospital length of stay or duration of mechanical ventilator. Additionally, hyperoxia was not associated with increased hospital stay (18.2% *vs.* 25.0%, p=0.2) Further, the hospital discharge GCS (10 ± 5 *vs.* 11 ± 4, p=0.1) and Glasgow outcome scores (3 ± 1 *vs.* 3 ± 1, p=0.35) were similar in hyperoxia and normoxia groups, respectively. The adjusted outcomes for different PaO_2 ranges in the first 3 h of intubation are presented in Figure 1A. Compared to a PaO_2 of 60 mmHg to 99 mmHg, there is no significant difference in hospital mortality or good neurological outcome (Glasgow outcome score ≥ 4) in any of the categories (100 mmHg to 200 mmHg, 201 mmHg to 300 mmHg, 301 mmHg to 400 mmHg, and >400 mmHg) (Table 3). In our multivariable logistic regression analysis, midline shift ≥ 5 mm was an independent predictor of mortality (OR: 0.19; 95% CI: 0.09 to 0.41, p<0.001), while hyperoxia was not associated with increased mortality (OR: 0.62, 95% CI 0.30 to 1.25, p=0.18). In subgroups analysis for hospital admission GCS<9, isolated TBI, initiation of HIP and PF ratio within first 3 h >300, there were no significant differences in both mortality and neurological outcomes between the groups.

Survivor *vs.* non-survivors analysis is presented in Table 4. Non-survivors had higher markers of severity (Injury Severity Score (ISS), Revised Trauma Score (RTS) and IMPACT mortality), and significantly lower oxygen saturation, temperature, and platelets. Further, non-survivors had lower median partial pressure of oxygen (165 mmHg, IQR 84 to 252 *vs.* 199 mmHg, IQR 111 to 329) and partial pressure to fractional inspired oxygen ratio (205 mmHg, IQR 112 to 337 *vs.* 299 mmHg, IQR 160 to 451) compared to survivors. Additionally, the frequency of hyperoxia (PaO_2>100 mmHg) was similar in survivors and non-survivors (77% *vs.* 70%, p=0.2, respectively).

The Kaplan-Meier curve (Figure 1B) compared the survival rates between the hyperoxia and normoxia groups. The log-rank test (p 0.06) indicated a no statistically significant difference between the groups for all-cause mortality.

Discussion

This retrospective study of moderate-severe TBI patients, suggests that hyperoxia (PaO_2>100 mmHg) in the first 3 h of admission was

Table 2: Clinical outcomes in normoxia and hyperoxia.

Variables	All N=308	Normoxia n=72	Hyperoxia n=236	P value
Duration on mechanical ventilator, days (mean ± SD)	10 ± 7	11 ± 6	10 ± 7	0.28
ICU Length of stay, days (mean ± SD)	15 ± 11	19 ±17	13 ± 9	<0.001
Hospital length of stay, days(median, IQR)	26 (11-59)	28 (10-67)	24 (11-55)	0.44
Tracheostomy, N (%)	98 (31.8)	29 (40.2)	69 (29.2)	0.07
ICU discharge GCS, (mean ± SD)	8 ± 4	7 ± 4	9 ± 4	0.02
Hospital discharge GCS, (mean ± SD)	11 ± 4	11 ± 4	10 ± 5	0.1
Hospital discharge GOS, (mean ± SD)	3 ± 1	3 ±1	3 ± 1	0.35
Hospital mortality, N (%)	61 (19.8)	18 (25.0)	43 (18.2)	0.2

SD: Standard Deviation; IQR: Interquartile Range; ICU: Intensive Care Unit; N: Patient Number; %: Patient Percentage; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Score

Table 3: Relationship of PaO_2 ranges on hospital mortality and GOS ≥ 4.

PaO_2 ranges	Total	Hospital mortality		Hospital discharge GOS ≥ 4	
	N (%)	OR	95% CI	OR	95% CI
60-99 mmHg	69 (22.4)	Reference		Reference	
100-200 mmHg	91 (29.5)	0.6	0.29-1.52	0.86	0.44-1.67
201-300 mmHg	63 (20.4)	0.66	0.29-1.52	0.65	0.30-1.36
301-400 mmHg	35 (11.6)	0.8	0.31-2.09	0.5	0.19-1.27
>400 mmHg	49 (15.9)	0.39	0.14-1.08	1.55	0.73-3.28

N: Number; %: Percentage; OR: Odds Ratio; CI: Confidence Interval; GOS: Glasgow Outcome Score

Table 4: Baseline characteristics of survivors and non-survivors.

Variables	All (N=309)	Survivors (N=235)	Non-survivors (N=73)	P value
Age, years (median IQR)	28 (23-36)	31 (12)	30 (11)	0.36
Male Gender, N (%)	292 (94.8)	236 (95.5)	56 (91.8)	0.23
IDBW, kg (mean ± SD)	65 ± 6	65 ± 6	64.7 ± 7	0.713
Markers of severity, (mean ± SD)				
Injury severity score	29 ± 7	29.5 ± 7	31.2 ± 7	0.03
Revised trauma score	5.3 ± 1.1	5.4 ± 1.1	4.7 ± 1.0	<0.001
IMPACT mortality	27.9 ± 17.8	24.4 ± 15.7	42.0 ± 19.4	<0.001
Vital signs at admission, (mean ± SD)				
MAP, mmHg	94 ± 27.5	94 ± 21	93 ± 27	0.88
Heart rate, beats/min	105 ± 28	105 ± 26	101 ± 34	0.27
Respiratory rate, breaths/min	24 ± 7	24 ± 6	23 ± 7	0.64
Oxygen saturation, %	96 ± 9	96 ± 7	91 ± 12	<0.001
Temperature, °C	36.7 ± 0.7	36.7 ± 0.6	36.4 ± 0.8	<0.001
Arrival GCS, N (%)				
GCS 9-12	56 (18)	52 (21.1)	4 (6.5)	0.009
GCS ≤ 8	252 (82)	195 (78.9)	57 (39)	
Laboratory parameters, (mean ± SD)				
Hemoglobin, gm/L	138 ± 25	139 ± 22	134 ± 32	0.13
Platelets, 109/L	272 ± 87	278 ± 88	245 ± 93	0.009
Creatinine, umol/L(median, IQR)	81 (71-960	80 (71-95)	84 (74-96)	0.84
Lactic Acid, mmol/L(median, IQR)	2.5 (1.5-4)	2.3 (1.3-3.8)	2.9 (1.9-4.7)	0.04
Respiratory parameters, (mean ± SD)				
Tidal volume per IDBW, mL/kg		6.5 ± 0.7	6.4 ± 0.7	0.18
FiO_2, %		0.7 (0.2)	0.8 (0.2)	0.03
PaO_2, mmHg (median, IQR)	194 (105-308)	199 (111-329)	165 (84-252)	0.04
PaO_2/FiO_2 ratio, (median, IQR)	267 (147-433)	299 (160-451)	205 (112-337)	0.02
Hyperoxia- PaO_2>100 mmHg, N (%)	236 (76)	193 (87)	43 (70)	0.2
CT head findings, N (%)				
Isolated head injury	96 (31)	73 (29.5)	23 (38)	0.21
Intraparenchymal Hemorrhage/Contusion	151 (49)	123 (49)	28 (46)	0.58
Midline Shift ≥ 5mm	42 (14)	21 (8.5)	21 (34)	<0.001
No findings on CT	50 (16)	46 (18)	4 (6)	0.02
Management, N (%)				
Tranexamic acid, N (%)	95 (31)	65 (26)	30 (49)	0.007
ICP Monitoring, N (%)	54 (17.5)	38 (14)	16 (25)	0.24
Hypertonic saline, N (%)	203 (67)	165 (53)	38 (56)	0.69
Head injury protocol, N (%)	215 (70)	162 (69)	53 (85)	0.08

SD: Standard Deviation; IMPACT: International Mission for Prognosis and Analysis of Clinical Trials; MAP: Mean Arterial Pressure; GCS: Glasgow Come Scale; IDBW: Ideal Body Weight; FiO_2: Fraction of Inspired Oxygen; PaO_2: Partial Pressure of Oxygen; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; ICP: Intracranial Pressure

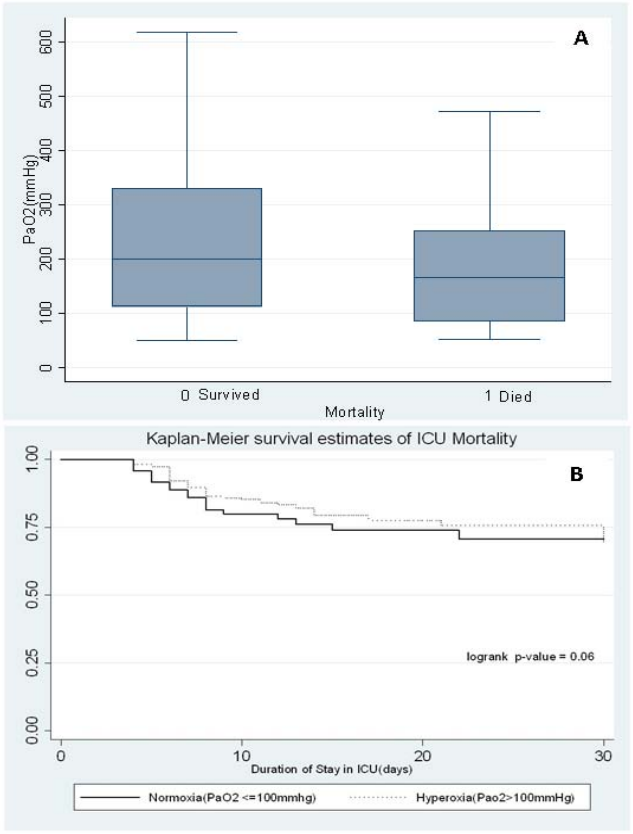

Figure 1: A) Association between PaO_2 and hospital mortality in an unadjusted analysis. B) Kaplan-Meier survival curve for normoxia verses hyperoxia.

not an independent predictor of hospital mortality or unfavorable neurological outcomes. In analyzing different ranges of PaO_2 none of the categories contribute to increased mortality or poor neurological outcomes. Further, in our survivors' *vs.* non-survivors analysis, hyperoxia was not associated with non-survival; rather survivors had a higher median PaO_2.

Comparing to Previous Literature

Supplemental oxygen therapy remains the cornerstone of many resuscitation protocols [17]. However, this frequently results in oxygen levels that exceed the patient physiological requirements. Substantial evidence suggests that elevated PaO_2 may increase the formation of reactive oxygen species in the neuronal tissue *via* the mitochondrial oxidoreductive process, which may enhance oxidative and nitrosative stress, thereby favoring the induction of apoptotic neuronal death and necrosis, potentially contributing to poor neurological outcomes [2]. Further, supra-physiological levels of oxygen can cause cerebral vasoconstriction resulting in decreased Cerebral Blood Flow (CBF), paradoxically lowering delivery of oxygen and other important substrates to the cerebral tissue [8]. Conversely, clinical studies suggest that supplemental oxygen seems to possess the potential to rescue threatened neurons after brain injury, and it is known to prolong the safe apnea time [20].

The metabolic demand of the brain increases immediately following TBI, but oxygen delivery may decrease due to a reduction of CBF, increased ICP, and decreased oxygen diffusion caused by capillary endothelium edema, secondary to the neuroinflammatory response [4]. This oxygen deficit forces conversion to anaerobic metabolism, resulting in depletion of cellular ATP. This crisis results in inadequate ATP needed for normal Na+/K+ ATPase pump function, leading to calcium influx, the release of excitatory neurotransmitters, and mediators of programmed cell death [5]. Hyperoxia has been associated with improvements in intracranial pressure, brain tissue oxygenation, lactate concentration, and lactate pyruvate ratio (creating a more aerobic metabolic profile) in TBI [21]. Ghosh et al. [6] showed that hyperoxia in acute brain injury resulted in increased brain tissue PaO_2, reduced lactate pyruvate ratio, increased cytochrome c oxidase, and cerebral metabolic rates.

This friend-foe dichotomy of oxygen therapy has made it challenging to ascertain the optimal targets for both SpO2 and PaO_2 in TBI patients. A large meta-analysis found increased rates of mortality for patients with oxygen saturation greater than 96% compared to 94% to 96%, but only one RCT on trauma patients was included and it showed no effects of liberal oxygen [22]. A recent meta-analysis by Ni et al. [19] found that hyperoxia did not contribute to higher mortality in patients with TBI (OR: 1.23, 95% CI 0.91 to 1.67; p=0.19), stroke (OR: 1.02, 95% CI 0.76 to 1.36; p=0.91), post-cardiac surgery (OR: 1.06, 95% CI 0.78 to 1.44; p=0.69) or mechanical ventilation (OR: 1.23, 95% CI 0.99 to 1.54; p=0.06), but was associated with higher mortality in post-cardiac arrest patients (OR: 1.30, 95% CI 1.08 to 1.57; p=0.03).

The results of our study are consistent with others, suggesting no association between hyperoxia and mortality or neurological outcome in TBI patients [2,15-17]. Raj et al. [15] using the Finnish intensive care consortium database of mechanically ventilated patients with moderate-to-severe TBI, found no independent relationship between hyperoxia (PaO_2>100 mmHg) and 6 month mortality (OR: 0.88, 95% CI 0.63 to 1.22; p=0.43) [15]. In patients with severe TBI, Russell and associates observed that hyperoxia in the first 24 h of intubation was not associated with increased mortality (OR: 1.27 95% CI 0.72 to 2.25; p=0.41) [2]. While, Fujita et al. [16] in a post-hoc analysis of data from the brain hypothermia study, revealed that PaO_2 was higher in survivors and those with favorable neurological outcomes as measured by GOS than in non-survivors and those with unfavorable outcomes (PaO_2: 242 *vs.* 193 mmHg, p=0.022 and PaO_2: 252 *vs.* 202 mmHg, p=0.008 respectively). Further, O'Brian et al. [20] found in 24,148 TBI patients that hyperoxia was not independently associated with greater in-hospital mortality in any group (OR: 0.99, 95% CI 0.84 to 1.13 - GCS<9; OR: 1.01 95% CI 0.67 to 1.51 - GCS 9 to 12; OR: 1.1 95% CI 0.75 to 1.63 - GCS>12) [17]. Recent data from a French registry of 5,912 patients, observed that early hyperoxia in trauma patients was associated with reduced adjusted in-hospital mortality (OR: 0.59 95% CI 0.50 to 0.70; p<0.0001) [20].

On the other hand, in patients with severe TBI Davis et al. [12] found that extreme hyperoxia (PaO_2 ≥ 487 mmHg) was associated with increased mortality (OR: 0.50, 95% CI 0.36 to 0.71, p<0.001). However, this study used an arbitrarily high PaO_2 as a threshold and only included the first PaO_2 measurement in their regression analysis models. Brenner et al. [14] in a single-center retrospective study, showed that hyperoxia (PaO_2>200 mmHg) was associated with increased hospital length of stay (OR: 0.75, 95% CI 0.60 to 0.94) and mortality (OR: 1.5, 95% CI 1.15 to 1.97; p=0.003), and decreased GCS (OR: 1.52, 95% CI 1.18 to 1.96; p=0.001). Although this study used the mean PaO_2 from ABGs in the first 24 h, it included non-mechanically ventilated patients, which may introduce biases, as it is possible that

patients not on mechanical ventilation had less severe TBI and thus less likely to be hyperoxic. Rincon and colleagues, in a multicenter cohort study of ventilated TBI patents found in a multivariate analysis that hyperoxia (PaO_2 ≥ 300 mmHg) was independently associated with higher in-hospital mortality (OR: 1.5, 95% CI 1.02 to 2.4; p=0.04) [13]. This study used only the "worst" PaO_2 which may be misleading as we found in our study that many patients may have an elevated PaO_2 immediately post-intubation, but this did not persist in subsequent ABGs repeated 1 to 3 h later.

In a randomized pilot study comparing FiO_2 of 0.7 (PaO_2 mean ± SD: 218 ± 92 mmHg) and FiO_2 of 0.4 (PaO_2 mean ± SD: 124 ± 42 mmHg), the higher fraction of FiO_2 was not associated with blood concentrations of markers of oxidative stress (reactive oxygen species-ROS), inflammation (Interleukin 6: Il6), neurological injury (Neuron-Specific Enolase: NSE), mortality (p=1.0) or poor neurological outcome (p=0.58) as measured by Extended Glasgow outcome scale [23].

Furthermore, the combination of hyperbaric and normobaric hyperoxia in the treatment of severe TBI has been associated with improved markers of oxidative stress, 26% absolute reduction in mortality (p=0.048), and 36% improvement in favorable outcome (p=0.024) [24]. This suggests that hyperoxia may contribute to increased oxygen delivery to brain tissue and protect against secondary ischemic damage [5].

Our subgroup analysis for patients with arrival GCS ≤ 8 and isolated TBI revealed that hyperoxia was not associated with increased hospital mortality or poor neurological outcomes. Analogous findings were reported by O'Brian et al. [17] in that hyperoxia was not identified as an independent risk factor for mortality in isolated TBI (OR: 1.21, 95% CI 0.90 to 1.64) or those with GCS<9 (OR: 0.99, 95% CI 0.84 to 1.13). Furthermore, different ranges of PaO_2 (50 mmHg to 99 mmHg, 100 mmHg to 200 mmHg, 201 mmHg to 300 mmHg, 301 mmHg to 400 mmHg, and >400 mmHg) were not associated with worse clinical outcomes.

This study did not find an exact threshold for either the SpO_2 or PaO_2 in TBI patients; however, it suggests that a moderately aggressive approach to maintaining PaO_2 above 100 mmHg does not seem to be harmful and may prevent episodes of hypoxia, which is known to be associated with increased mortality in TBI [25,26]. Hence, any theoretical disadvantage caused by increased free radical and oxygen toxicity may be outweighed by the beneficial effect of improved tissue oxygenation, thus avoiding hypoxia.

Strength and Limitation

This study has several strengths including the use of a relatively large well-designed database to extract patients with moderate-severe TBI as the data were collected by trained collectors and have been validated. We included only patients receiving mechanical ventilation, with multiple ABGs with the first 48 h of intubation, ensuring that the cohort had a significant injury and remained hyperoxic for several hours. We used validated markers for severity of illness, which allowed us to calculate adjusted mortality risk with varying PaO_2 categories. We also performed analysis in multiple subgroups to further substantiate our findings. Lastly, we used Glasgow outcome sores to evaluate neurological outcomes. Regardless of this However, we acknowledge several limitations to this study. Firstly, this was a single-centered study of mostly male patients, thus generalization of our findings should be cautious. Secondly, this was an observational study, in which we did not collect information on other factors that could influence the analysis such as unmeasured confounder. Third, due to the retrospective nature of the study we were unable to assess long-term neurological outcome and our GOS was done at hospital discharge. Finally, TBI encompasses a number of unique pathologies (e.g., SDH, SAH, diffuse axonal injury) and that although no differences were evident in isolated TBI and GCS ≤ 8, it is highly conceivable that hyperoxia may impact each injury sub-type differently.

Conclusion

Our data revealed that hyperoxia (PaO_2>100 mmHg) was not associated with increased mortality or poor neurological outcomes (determined by GOS) in moderate-severe TBI patients. Further, our analysis did not reveal any PaO_2 range 100 mmHg to 200 mmHg, 201 mmHg to 300 mmHg, 301 mmHg to 400mmHg, and >400 mmHg) for which outcomes were affected. Thus, currently the exact target for SaO_2 and PaO_2 in TBI remains unclear, and requires clear evidence from well-designed randomized control studies.

References

1. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9(4):231-6.
2. Russell DW, Janz DR, Emerson WL, May AK, Bernard GR, Zhao Z, et al. Early exposure to hyperoxia and mortality in critically ill patients with severe traumatic injuries. BMC Pulm Med. 2017;17(1):29.
3. Vella MA, Crandall ML, Patel MB. Acute management of traumatic brain injury. Surg Clin North Am. 2017;97(5):1015-30.
4. Abate MG, Trivedi M, Fryer TD, Smielewski P, Chatfield DA, Williams GB, et al. Early derangements in oxygen and glucose metabolism following head injury: The ischemic penumbra and pathophysiological heterogeneity. Neurocrit Care. 2008;9(3):319-25.
5. Daly S, Thorpe M, Rockswold S, Hubbard M, Bergman T, Samadani U, et al. Hyperbaric oxygen therapy in the treatment of acute severe traumatic brain injury: A systematic review. J Neurotrauma. 2018;35(4):623-9.
6. Ghosh A, Highton D, Kolyva C, Tachtsidis I, Elwell CE, Smith M. Hyperoxia results in increased aerobic metabolism following acute brain injury. J Cereb Blood Flow Metab. 2017;37(8):2910-20.
7. Page D, Ablordeppey E, Wessman BT, Mohr NM, Trzeciak S, Kollef MH, et al. Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: A cohort study. Crit Care. 2018;22(1):9.
8. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. J Appl Physiol (1985). 2003;95(6):2453-61.
9. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: Prospective multicenter protocol-directed cohort study. Circulation. 2018;137(20):2114-24.
10. Stolmeijer R, Bouma HR, Zijlstra JG, Drost-de Klerck AM, Ter Maaten JC, Ligtenberg JJM. A systematic review of the effects of hyperoxia in acutely ill patients: Should we aim for less? Biomed Res Int. 2018;2018:7841295.
11. Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M. Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. Neurocrit Care. 2015;22(2):243-50.
12. Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009;26(12):2217-23.

13. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: A multicentre cohort study. J Neurol Neurosurg Psychiatry. 2014;85(7):799-805.

14. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg. 2012;147(11):1042-6.

15. Raj R, Bendel S, Reinikainen M, Kivisaari R, Siironen J, Lang M, et al. Hyperoxemia and long-term outcome after traumatic brain injury. Crit Care. 2013;17(4):R177.

16. Fujita M, Oda Y, Yamashita S, Kaneda K, Kaneko T, Suehiro E, et al. Early-stage hyperoxia is associated with favorable neurological outcomes and survival after severe traumatic brain injury: A post-hoc analysis of the brain hypothermia study. J Neurotrauma. 2017;34(8):1565-70.

17. D OB, Nickson C, Pilcher DV, Udy AA. Early hyperoxia in patients with traumatic brain injury admitted to intensive care in Australia and New Zealand: A retrospective multicenter cohort study. Neurocrit Care. 2018;29(3):443-51.

18. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: A systematic review, meta-analysis, and meta-regression of cohort studies. Crit Care Med. 2015;43(7):1508-19.

19. Ni YN, Wang YM, Liang BM, Liang ZA. The effect of hyperoxia on mortality in critically ill patients: A systematic review and Meta analysis. BMC Pulm Med. 2019;19(1):53.

20. Baekgaard JS, Abback PS, Boubaya M, Moyer JD, Garrigue D, Raux M, et al. Early hyperoxemia is associated with lower adjusted mortality after severe trauma: Results from a French registry. Crit Care. 2020;24(1):604.

21. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia--induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: A prospective historical cohort-matched study. J Neurosurg. 2004;101(3):435-44.

22. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis. Lancet. 2018;391(10131):1693-705.

23. Lang M, Skrifvars MB, Siironen J, Tanskanen P, Ala-Peijari M, Koivisto T, et al. A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress. Acta Anaesthesiol Scand. 2018;62(6):801-10.

24. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg. 2013;118(6):1317-28.

25. Asher SR, Curry P, Sharma D, Wang J, O'Keefe GE, Daniel-Johnson J, et al. Survival advantage and PaO2 threshold in severe traumatic brain injury. J Neurosurg Anesthesiol. 2013;25(2):168-73.

26. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma. 1993;34(2):216-22.