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A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress

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Conflict of interest
Authors have no conflict of interests.

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Background: Normobaric hyperoxia is used to alleviate secondary brain ischaemia in patients with traumatic brain injury (TBI), but clinical evidence is limited and hyperoxia may cause adverse events.
Methods: An open label, randomised controlled pilot study comparing blood concentrations of reactive oxygen species (ROS), interleukin 6 (IL-6) and neuron-specific enolase (NSE) between two different fractions of inspired oxygen in severe TBI patients on mechanical ventilation.
Results: We enrolled 27 patients in the Fi O_2 0.40 group and 38 in the Fi O_2 0.70 group; 19 and 23 patients, respectively, completed biochemical analyses. In baseline, there were no differences between Fi O_2 0.40 and Fi O_2 0.70 groups, respectively, in ROS (64.8 nM [22.6–102.1] vs. 64.9 nM [26.8–96.3], $P = 0.80$), IL-6 (group 92.4 pg/ml [52.9–171.6] vs. 94.3 pg/ml [54.8–133.1], $P = 0.52$) or NSE (21.04 ug/l [14.0–30.7] vs. 17.8 ug/l [14.1–23.9], $P = 0.35$). ROS levels did not differ at Day 1 (24.2 nM [20.6–33.5] vs. 29.2 nM [22.7–69.2], $P = 0.10$) or at Day 2 (25.4 nM [21.7–37.4] vs. 47.3 nM [34.4–126.1], $P = 0.95$). IL-6 concentrations did not differ at Day 1 (112.7 pg/ml [65.9–168.9) vs. 83.9 pg/ml [51.8–144.3], $P = 0.41$) or at Day 3 (55.0 pg/ml [34.2–115.6] vs. 49.3 pg/ml [34.4–126.1], $P = 0.95$). NSE levels did not differ at Day 1 (15.9 ug/l [9.0–24.3] vs. 15.3 ug/l [12.2–26.3], $P = 0.62$). There were no differences between groups in the incidence of pulmonary complications.
Conclusion: Higher fraction of inspired oxygen did not increase blood concentrations of markers of oxidative stress, inflammation or neurological injury or the incidence of pulmonary complications in severe TBI patients on mechanical ventilation.

Editorial comment
While hypoxia must be avoided to limit or prevent secondary injury in patients with traumatic brain injury, there is limited evidence to support benefit of hyperoxia. The results of the first 65 patients in a randomised, controlled trial of high (0.7) versus low (0.4) fractions of inspired oxygen did not demonstrate any clear differences in oxidative stress, inflammation, or injury markers.

Traumatic brain injury (TBI) is the leading cause of death in young people,[1] and disability is a severe problem among survivors.[2–4]In TBI patients, regional brain ischaemia is a common finding, which may be related to low tissue oxygen tension ($PtiO_2$).[5,6]The use of high fractions of inspired oxygen is one intervention used to correct low $PtiO_2$. Moderate hyperoxia increases the cerebral aerobic metabolism[7] and has been suggested as a means of improving outcomes after TBI.[7–9]Experimental studies indicate that normobaric hyperoxia improves the perilesional tissue metabolic rate of oxygen.[10,11] On the other hand, normobaric hyperoxia is associated with increased cerebral excitotoxity[12] and increased PaO_2 has direct vasoconstrictive effect on arterioles that in turn reduces cerebral blood flow.[13] One mechanism by which oxygen toxicity occurs is the production and accumulation of excessive reactive oxygen species (ROS),[14–16] which can potentially exacerbate brain injury.[17] Furthermore, TBI is associated with the activation of several inflammatory pathways, which may be modulated by the amount of oxygen available in tissue. The effects of hyperoxia on inflammation are not well understood: normobaric hyperoxia increases inflammatory marker release,[18] whereas hyperbaric hyperoxia has been shown to reduce levels of the proinflammatory marker interleukin 6 (IL-6)[19], which is associated with the neurological outcome.[18] However, using a high fraction of inspired oxygen has also been associated with pulmonary adverse events, such as ventilation–perfusion mismatch, pulmonary oedema and inflammation.[20] A high concentration of inspired oxygen may cause the formation of lung atelectasis, and some studies even suggest an increase in mortality in general intensive care unit (ICU) patients.[19,21] There are no clinical studies on the effect of the prolonged use of normobaric hyperoxia on inflammatory markers, markers of oxidative stress and neurological injury in TBI. Accordingly, in this pilot study, we compared the effect of a ventilation strategy aiming at moderate hyperoxaemia (FiO_2 0.70) to a standard oxygen fraction (FiO_2 0.40) in patients with severe traumatic brain injury (Glasgow Coma Score (GCS)< 8). We hypothesised that a strategy using a higher oxygen fraction would result in an alleviated inflammatory response and lower markers of neurological injury, without significantly increasing oxidative stress.

Materials and methods

Trial design, participants and setting

Trial design

BRAINOXY was a randomised, controlled, open label pilot study comparing 0.70 and 0.40 oxygen in mechanically ventilated intensive care patients with severe traumatic brain injury. The pilot study was performed in three Finnish intensive care units (ICUs): Kuopio University Hospital (KUH), Tampere University Hospital (TAYS) and Helsinki University Central Hospital, Töölö Hospital (HUCH) during the period of December 2010 to September 2013. The inclusion criteria were as follows:

isolated non-penetrating TBI or multiple trauma patient with TBI with Glasgow coma scale (GCS) eight or less (inclusive), expected need for intubation and mechanical ventilation > 24 h, recruitment within 18 h after admission to ICU and time from TBI < 36 h and informed consent from next of kin.

Exclusion criteria were as follows: age < 18 or > 65 years, anticipated brain death in 12 h or otherwise moribund patient expected to die in 24 h, expected need for mechanical ventilation < 24 h, insufficient oxygenation assessed by a clinician or multiple trauma patients with brain injury and severe abdominal, thoracic or pelvic injury possibly affecting oxygenation, no consent, insufficient oxygenation with the treatment modality of the lower oxygenation group (Pa02 < 13 kPa or SpO_2 < 95% with Fi02 0.40 and PEEP of 10) or oxygenation failure probable during ICU care, penetrating TBI, suspected pregnancy (perform urinary or serological pregnancy test if suspected).

Randomisation procedure

We used sealed, opaque envelopes to randomly divide patients into two intervention groups. Patients were stratified according to TBI severity (group GCS 3–5 and group GCS 6–8), whether they had a surgically removed haematoma prior

to ICU admission or diffuse brain injury, or whether they had decompressive craniectomy performed prior to randomisation. Patients had to be included within 36 h from injury and 18 h from admission to ICU. To exclude those patients with a GCS< 8 due to a concomitant intoxication and those who regained consciousness immediately following operative treatment, a sedation break was performed in the ICU and this measured GCS was used as the inclusion criterion.

Study intervention

Patients were randomly assigned to receive either FiO_2 0.40 or 0.70 of inspired oxygen during the period of mechanical ventilation for a maximum time of 14 days. Fi 0.40 and Fi 0.70 groups were chosen by a consensus decision in the study management committee. Positive end expiratory pressure (PEEP) of 8–10 was used to minimise lung atelectasis. Otherwise, the patient treatment was at the discretion of the treating clinician, but it was recommended that the Brain Trauma Foundation Guidelines be followed (Appendix S1).

Laboratory sample handling and analysis

Laboratory samples were centrifuged and frozen at −70°C. Serum was used for NSE analyses and plasma for IL-6, ROS and RNS analyses.

Neuron-specific enolase was analysed with electrochemiluminescence immunoassay (ECLIA). The reagent used in analysis was neuron-specific enolase (NSE) (catalogue number 12133113 122, Roche Diagnostics GmbH, Mannheim, Germany) and the instrumentation used was the Cobas e 601 analyser (Hitachi High Technology Co., Tokyo, Japan). The NSE was analysed only once. This methodology is in clinical practise and our accredited Kuopio University Hospital laboratory analysed all samples. The concentration of IL-6 in the plasma was measured using a Sandwich enzyme-linked immunosorbent assay (ELISA) kit (BioLegend, San Diego, CA, USA) and the data were calculated with computer-based, curve-fitting software, after which the concentrations of the samples were multiplied by the appropriate dilution factor (1 : 1). IL-6 was measured in duplicate.

Reactive oxygen species and RNS plasma levels were measured using the OxiSelect™ In Vitro ROS/RNS Assay Kit (Cell Biolabs, Inc., San Diego, CA, USA). All the patients were sedated with propofol. Glycerol is an ingredient in propofol solution. In this analysis, the concentration of glycerol in propofol was 2.5% and in the compactible concentration range below 10%. The ROS assay was performed as per the manufacturer's instructions. ROS and RNS were measured in duplicates.

Outcome variables and statistical considerations

Originally, when this study was designed, the primary intention was to evaluate neurological outcome at 6 months. Power analysis based on a risk of poorer outcome than expected (death or severe neurological injury) with 80% power at 5% significance level resulted at sample size of 500 patients (250 patients in both oxygen groups) to detect a 10% decrease in poor outcome. However, owing to a lack of funding and a slow recruitment rate, the study is presented as a pilot study with laboratory markers as the surrogate outcome during the three-first days. The analysis plan was approved in advance by all authors. The agreed primary outcomes for this were the levels of ROS, IL-6 and NSE over time during ICU care. It was decided to focus on patients remaining in the ICU for longer than 40 h. Post hoc power analysis (power 80% and $P = 0.05$) based on mean values and standard deviation of ROS/RNS values on Day 1 gave a sample size of 123 patients.

Data collection

Data were collected with paper case record forms (CRF), which included patient demographics, comorbidities, medications, pre-hospital treatment with relevant time points, clinical status at arrival and type of trauma. Daily data collection in the ICU included vital signs, neurological status and acute physiology and chronic health evaluation (APACHE II).[22] Also recorded were sequential organ failure assessment (SOFA),[23] chest X-rays, head computer tomography (CT) classification according to the Marshall classification,[24] fluid balance, blood transfusion and interventions aiming at decreasing intracranial pressure, daily blood samples

(arterial blood gases at least three times a day) and respiratory management (ventilatory settings, PaO_2 : FiO_2 ratio and static compliance). Study-specific laboratory markers ROS/RNs, IL-6 and NSE were measured at admission, Day 1 and/or Days 2 and 3. The Extended Glasgow Outcome Scale (GOSE)[25] was assessed by a blinded neurologist at 6 months, after contacting the patient or patient's representative by phone.

Statistical analysis

Categorical data are presented as absolute numbers, with percentages in parentheses. For comparing categorical data, we used a two-sided chi-squared test or Fisher's exact test when appropriate. We tested all continuous data for skewness, and these data are presented as medians with interquartile ranges (IQR), unless stated otherwise. We used the non-parametric Mann–Whitney *U*-test for univariate comparison. Group levels of ROS, IL-6 and NSE over time were compared by a linear mixed model, using a variance component structure. The change of ROS, IL-6 and NSE levels in the groups over time was compared using the non-parametric Friedman test (three time points) or Wilcoxons signed-rank test (two time points). We used statistical software SPSS version 22 (IBM SPSS Statistics, Armonk, NY, USA).

Ethical considerations

This pilot study was conducted according to the principles of the Helsinki Declaration. The ethics committee of Northern Savo, Finland approved the study protocol number 93/2009. Informed consent was obtained by the patient representative prior to the study intervention. If the patient regained capacity to give informed consent, a deferred patient consent was obtained.

Results

Of a total of 380 screened patients, 65 patients were included, with 27 (42%) randomised to the FiO_2 0.40 group and 38 (58%) to the FiO_2 0.70 group (Fig. 1). Altogether, 23 study patients had incomplete laboratory tests at Day 2 or 3 and were subsequently excluded from the analysis of laboratory markers, but their clinical outcomes are presented. Patient baseline characteristics are presented in Table 1. The mean patient age was 43 + 17 years in the FiO_2 0.4 group and 45 + 13 in the FiO_2 0.70 group ($P = 0.97$). Admission SOFA and APACHE II scores were equal in both groups and no statistical differences in the admission GCS were observed (Table 1). The haemoglobin concentration was lower in the FiO_2 0.70 group (125 + 2 g/l) than in the FiO_2 0.40 group (131 + 2 g/l, $P = 0.02$). The risk of poor outcome and death calculated with The International mission for prognosis and analysis of clinical trials in TBI prognostic calculator (TBI-IMPACT)[26] was higher in the FiO_2 0.70 group that FiO_2 0.40 group, respectively (0.56 + 0.20 vs. 0.45 + 0.15, $P < 0.03$ and 0.35 + 0.16 vs. 0.25 + 0.15, $P < 0.02$). In the FiO_2 0.70 group, there were more patients with poor GCS and a mass lesion in CT-scan Table 1).

Study intervention

In the FiO_2 0.40 group, the mean FiO_2 was 0.42 and in the FiO_2 0.70 group it was 0.68 ($P < 0.001$). The median length of the study intervention was 213 (116–318) h in the FiO_2 0.40 group and 120 (64–159) h in the FiO_2 0.70 group ($P = 0.10$). Patients in the FiO_2 0.40 group had a longer length of ICU stay than patients in the FiO_2 0.70 group (273 [139–414] h vs. 156 h [110–274], respectively) ($P = 0.03$). Patients in the higher oxygen group had significantly higher mean arterial blood oxygen tension than patients in the lower oxygen group ($P < 0.001$). A higher oxygen fraction resulted, as expected, in significantly higher mean oxygen tension, without differences in mean carbon dioxide (Table 2, Fig. 2). The oxygen tension in arterial blood was 16.59 kPa in the FiO_2 0.40 group and 29.09 kPa in the FiO_2 0.70 group ($P < 0.001$).

Differences in laboratory markers

Blood levels of ROS, IL-6 and NSE are shown in Fig. 3. The number of patients in FiO_2 0.40 group is 19 and the number of patients in FiO_2 0.70 group is 23. The time delay from trauma to

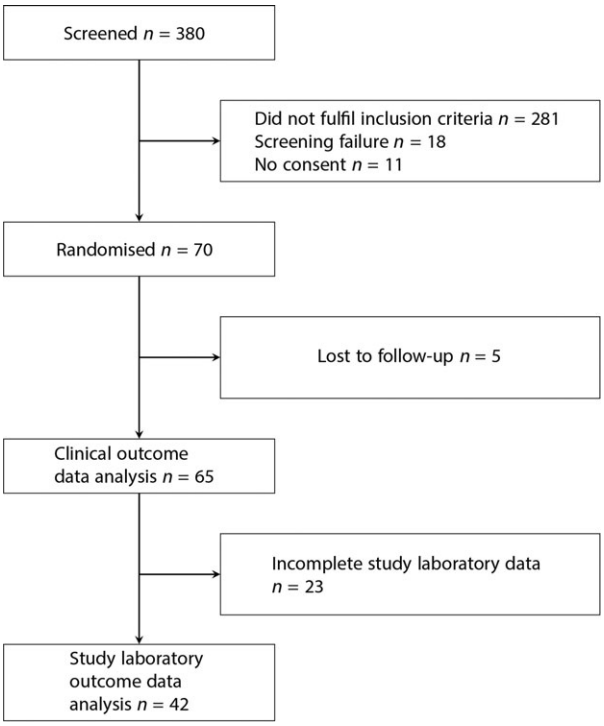

Fig. 1. Study flowchart.

first blood sampling in FiO_2 0.40 group was 12 h (7–23) and in FiO_2 0.7 group 17 h (11–24), $P = 0.16$. The first time point on the blood samples was taken in 24 h intervals. ROS concentrations were similar at admission, that is, 64.8 nM (22.6–102.1) in the FiO_2 0.40 group and 64.9 nM (26.8–96.3) in the FiO_2 0.70 group ($P = 0.80$). ROS concentrations were also similar at Day 1, 24.2 nM (20.6–33.5) in the FiO_2 0.40 group and 29.2 nM (22.7–69.2) in the higher group ($P = 0.10$). At Day 2, ROS concentrations were 25.4 nM (21.7–37.4) in the FiO_2 0.40 group and 47.3 nM (34.4–126.1) in the FiO_2 0.70 group ($P = 0.95$).

IL-6 concentrations were 92.4 pg/ml (52.9–171.6) in the FiO_2 0.40 group and 94.3 pg/ml (54.8–133.1) in the higher inspired oxygen group ($P = 0.52$). At Day 1, there were no significant differences in IL-6 concentrations between the lower group (112.7 pg/ml [65.9–168.9]) and the FiO_2 0.70 group (83.9 pg/ml [51.8–144.3]) ($P = 0.41$). At Day 3, the IL-6 concentrations were similar in the lower group (55.0 pg/ml [34.2–115.6]) and the higher group (49.3 pg/ml [34.4–126.1]) ($P = 0.95$).

NSE concentrations in both groups were similar at admission (FiO_2 0.40 group 21.04 ug/l [14.0–30.7] vs. FiO_2 0.70 group 17.8 ug/l [14.1–23.9]) ($P = 0.35$). At Day 1, the NSE concentration was 15.9 ug/l (9.0–24.3) in the FiO_2 0.40 group and 15.3 ug/l (12.2–26.3) in the FiO_2 0.70 group ($P = 0.62$).

Pulmonary complications and clinical outcomes

The incidence of acute respiratory distress syndrome (ARDS), atelectasis formation and pneumonia were similar in both groups (ARDS $P = 0.067$, atelectasis formation $P = 0.722$ and pneumonia $P = 0.534$). The P/F-ratio was similar in both groups, $P = 0.113$ (Table 2, Figure S1).

Discussion

Key findings

In this pilot study conducted in mechanically ventilated patients with severe TBI, the use of an inspired oxygen fraction of 0.70 compared to 0.40 did not increase markers of oxidative stress, inflammation or neurological injury, measured by levels of ROS, IL-6 and NSE. Although the study is underpowered, the results suggest that the use of a higher oxygen fraction is safe and does not result in more pulmonary complications or a prolonged need for mechanical ventilation. Future studies are warranted to clarify the role of normobaric hyperoxia in TBI patients.

Comparison to previous studies

Exposure to hyperoxia has been investigated in both animal and human studies. In animal studies, the effects of hyperoxia are contradictory. In animal brain injury and ischaemia resuscitation models, Ahn and by Hazeltom showed that hyperoxia results in an increased inflammatory response and that normoxaemia reduces oxidative damage to the brain, measured by levels of ROS.[17,27]In these studies, the animals were exposed to hyperoxia for 1 h only. The vast majority of animal studies suggest that short periods of hyperoxia do not promote additional

Table 1 Baseline characteristics.

	FiO_2 0.40 n = 27 (42%)	FiO_2 0.70 n = 38 (58%)	P
Patient characteristics			
Age, years	43 + 17	45 + 13	0.971
Gender, M/F	23/4	31/7	0.751
Height, cm	178 (175–180)	180 (170–181)	0.558
Weight, kg	82 + 15	79 + 13	0.516
Comorbidities			
Heart disease	6	7	0.706
Neurological disease	1	2	0.628
Pulmonary disease	1	5	0.197
Diabetes	6	9	0.991
Anticoagulation therapy	1	1	0.152
Severity of TBI			
Pupils			
Both reacting	19	25	0.839
One reacting	7	10	
Both unreactive	1	2	
Pre-hospital hypoxia, SpO_2 < 90%	5 (19%)	10 (26%)	0.569
Pre-hospital hypotension, SAP < 90 mmHg	5 (19%)	2 (5%)	0.612
Worst GCS within 24 h from admission			
3	10	20	0.667
4	5	7	
5	5	3	
6	3	3	
7	3	2	
8	1	2	
Marshall CT category			
1	0	0	0.443
2	8	6	
3	4	5	
4	2	2	
5	4	4	
6	8	20	
Hb concentration g/l on admission	131 + 19	125 + 22	0.020
Risk of poor outcome (TBI-IMPACT)	0.45 + 0.21	0.56 + 0.20	0.033
Risk of death (TBI-IMPACT)	0.25 + 0.15	0.35 + 0.16	0.016
Delay from trauma to neurosurgical ICU, h	2 (1–4)	4 (2–10)	0.824
General severity of illness			
SOFA	10 + 2.7	10 + 2.8	0.277
APACHE II	22 + 5	23 + 5	0.342
Blood glucose on admission mg/l	7.8 + 2.9	8.2 + 3.1	0.985
Thrombocyte count on admission × 10^3/μl	197 (148–227)	192 (133–241)	0.917

Continuous data are presented as mean (SD) or median (IQR). For normally distributed data, the χ2-test (Bonferroni correction) was used and, when the expected value was below 5, the Fischer's exact test was used. For non-parametric continuous data, the Mann–Whitney U-test was used. SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SAP, systolic blood pressure; MAP, mean arterial pressure; eGOSE, extended Glasgow Outcome Scale; TBI-IMPACT, International mission for prognosis and analysis of clinical trials in TBI prognostic calculator.

free radical production,[28] and the effects of hyperoxia on oxidative stress seem to be time-dependent. In the present pilot study, although the exposure to hyperoxia lasted for 165 + 108 h, we failed to show any difference in the oxidative stress between groups. Fujita et al[9] studied the effect of early-stage hyperoxaemia on neurological outcome in patients with

Table 2 Study outcomes.

	FiO_2 0.40, *n* = 27 (42%)	FiO_2 0.70, *n* = 38 (58%)	*P*
Arterial blood gases			
PaO_2 kPa	16.59 + 5.66	29.09 + 12.34	< 0.001
$PaCO_2$ kPa	4.71 + 0.91	4.65 + 0.81	0.9
Pulmonary function			
P/F ratio	338 + 76	367 + 68	0.113
ARDS (*n*)	3	0	0.067
Atelectasis formation (*n*)	14	18	0.722
Pneumonia (*n*)	6	6	0.534
Outcome			
Length of mechanical ventilation, h	151 (113–240)	121 (59–180)	0.441
Length of ICU stay, h	273 (139–414)	156 (110–274)	0.029
Length of hospital stay, h	374 (279–638)	277 (135–479)	0.116
Death (*n*)	8	9	1.00
eGOSE at 6 months (*n*)			
Good (7–8)	3	8	0.583
Moderate (2–6)	15	19	
Poor (1–2)	8	10	

Continuous data are presented as mean (SD) or median (IQR). For normally distributed data, the χ^2-test (Bonferroni correction) was used and, when the expected value was below 5, the Fischer's exact test was used. For non-parametric continuous data, the Mann–Whitney *U*-test was used. SD, standard deviation; IQR, interquartile range; P/R ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; ICU, intensive care unit; ARDS, Acute respiratory distress syndrome; eGOSE, Extended Glasgow outcome scale.

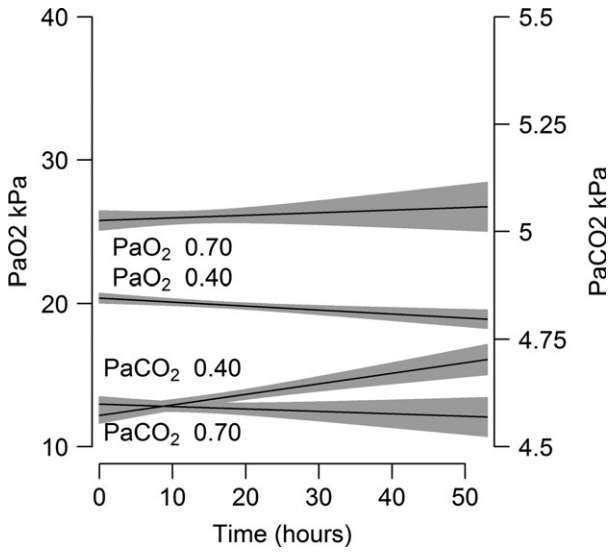

Fig. 2. The mean and standard deviation of tension of oxygen and carbon dioxide in the intervention groups.

TBI. They found hyperoxia to be beneficial in terms of neurological outcome and survival although the intervention lasted for only 24 h and these patients were either fever controlled or experiencing mild hypothermia.

Most studies on hyperoxia in patients with TBI are retrospective and assess the impact of hyperoxia on the crude outcome. Generally, hyperoxia is associated with increased mortality, but the interpretation of such results is challenging, owing to the heterogeneity of the studies.[29]

In humans, Puccio et al[30] studied the effect of hyperoxia on patients with severe TBI. They ventilated the patients for 2 h with FiO_2 1.0 and found that hyperoxia did not increase oxidative stress markers. This is in accordance with our pilot study, which suggests that even prolonged exposure to higher oxygen does not increase oxidative stress, inflammation or neurological injury.

The association of oxidative stress and inflammation is complex. In in vitro models, hyperoxia has been shown to increase ROS, which in turn results in the generation of intracellular inflammatory markers such as IL-6 and IL-8 in lung tissue.[15] Theoretically, hyperoxia-induced lung injury results from direct oxygen toxicity and the accumulation of inflammatory mediators in the lung tissue.[15] Hyperoxia-induced lung injury (HALI) is proportional to PaO_2 and exposure duration.[31] However, the duration of

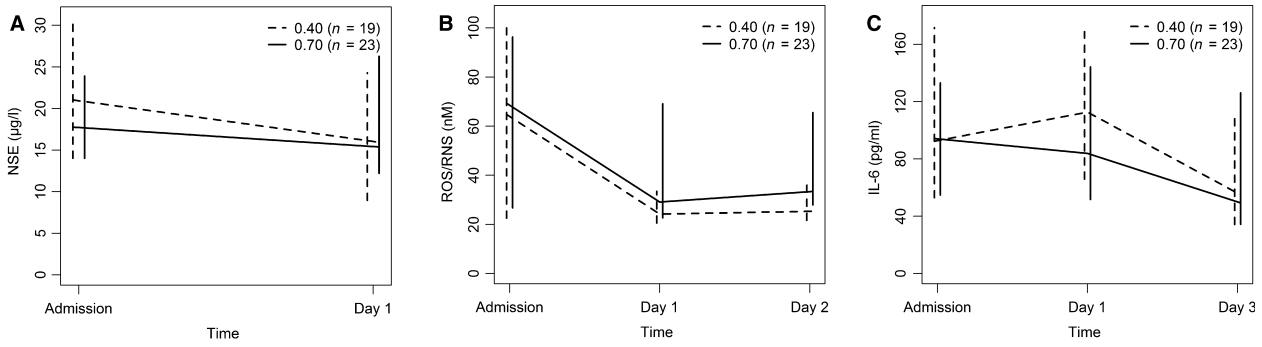

Fig. 3. A, B, C Median and interquartile range blood levels of neuron-specific enolase (NSE), reactive oxygen species (ROS/RNS) and interleukin-6 (IL-6).

hyperoxia leading to pulmonary toxicity is unknown.[32] Conservative oxygen therapy is associated with less radiological atelectasis formation, but its clinical impact is unclear.[33] In a retrospective observational study, hyperoxia was independently associated with ventilator-induced pneumonia,[34] but another study found that hyperoxia did not affect ICU or hospital length of stay.[35] The present pilot study did not exhibit any adverse effects of hyperoxia on lungs; indeed, to the contrary, the FiO_2 0.40 group had a longer ICU length of stay.

It must be kept in mind that neuroinflammation has both beneficial and detrimental effects on the brain after TBI. It promotes the reparation and regeneration processes of the primary injury; on the other hand, it may worsen secondary brain injury.[36] In our pilot study, even NSE concentrations were equal in both study groups, suggesting that hyperoxia in this complex setting does not negatively affect brain tissue.

We are not aware of any other randomised studies with severe TBI in which hyperoxia has been studied to a standard of FiO_2 of 0.40. Generally, conservative oxygen therapy is associated with a shorter duration of mechanical ventilation[33,37]and more ventilator-free days, without an impact on ICU mortality.[37] The present pilot study was unable to confirm these findings.

Limitations

First, the present pilot study was designed to be a randomised controlled trial with a patient-centred outcome as the endpoint. However, owing to lack of funding and slow recruitment, the study was terminated and is therefore study is presented as a pilot study with laboratory markers as primary outcome. Secondly, there was a difference in severity of TBI according to the TBI-IMPACT model between groups, and this may have influenced the study findings.

Conclusion

In the current pilot study, prolonged use of an inspired fraction of oxygen of 0.70 compared to 0.40 did not affect the blood levels of markers of oxidative stress, inflammation or neurological injury. In addition, we found no difference in pulmonary complications between the groups. Further studies are needed to evaluate the impact of using higher oxygen fractions on neurological outcome after severe TBI.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Head Injury Management Guidelines.
Figure S1. Mean and standard deviation of P/F-ratio in the intervention groups.