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EXAMINING BRAIN TISSUE OXYGEN LEVELS AND METABOLIC ACTIVITY IN FOCAL AND DIFFUSE TRAUMATIC BRAIN INJURY: A CROSS-SECTIONAL STUDY.

*Md Mohsin Hashmi**
MBBS MD, Department of Neurologist, Tianjin Medical University, China

ABSTRACT.

Background:
The study aimed to determine if the response pattern varied based on the type of injury and probe location by examining cerebral metabolism and oxygen levels using microdialysis (MD) and the novel near-infrared spectroscopy (NIRS) probe.

Methods:
The cross-sectional study included twenty Traumatic Brain Injury (TBI) patients with a Glasgow Coma Scale score of ≤8 was included. Advanced neuromonitoring techniques, including microdialysis and brain tissue oxygenation monitoring, were employed to assess cerebral metabolism and oxygen levels. Statistical analysis involved mean, standard deviations, ANOVA, and Mann–Whitney U test.

Results:
The study included 20 TBI patients (mean age 45 ± 10 years, predominantly male). Mean intracranial pressure (ICP) was 18.5 ± 4.2 mmHg, and cerebral perfusion pressure (CPP) was 65.2 ± 5.8 mmHg. Brain tissue oxygenation (BtipO2) averaged 22.6 ± 3.5 mmHg. Significant differences in BtipO2 were found between focal (25.0 ± 3.0 mmHg) and diffuse TBI (18.0 ± 2.5 mmHg) ($p < 0.05$). Higher BtipO2 was observed with ICP < 20 mmHg and CPP > 60 mmHg. Microdialysis showed varying levels of lactate (4.2 ± 1.0 mmol/L), pyruvate (1.8 ± 0.5 mmol/L), glucose (2.5 ± 0.7 mmol/L), glutamate (10.3 ± 2.2 µmol/L), and glycerol (0.6 ± 0.3 µmol/L). Further Mann-Whitney U tests showed notable BtipO2 fluctuations at specific intervals.

Conclusion:
Comprehensive monitoring of intracranial parameters and cerebral metabolism provides crucial insights for TBI management. Tailored treatment strategies guided by advanced neuromonitoring techniques can improve patient outcomes by addressing brain tissue vulnerability and metabolic disturbances.

Recommendations:
It is recommended to integrate advanced neuromonitoring techniques into routine TBI management protocols. Personalized treatment approaches based on individual patient profiles should be implemented.

Keywords: *Brain Tissue Oxygenation, Traumatic Brain Injury, Microdialysis, Neuromonitoring, Intracranial Parameters*
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Corresponding author: *Md Mohsin Hashmi**
Email: *drmdmohsinhashmi@gmail.com*
MBBS MD, Department of Neurologist, Tianjin Medical University, China

INTRODUCTION.

Traumatic Brain Injury (TBI) is a complex medical challenge that affects millions of individuals annually, necessitating a nuanced understanding of its pathophysiology for effective management. A critical aspect of TBI treatment involves monitoring brain tissue oxygen levels and metabolic activity, which differ significantly between focal and diffuse types of injuries.

Brain tissue oxygenation (BtipO2) is particularly telling in the management of TBI, serving as a vital indicator of the brain's vulnerability. This parameter provides crucial information beyond traditional metrics such as intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Studies have shown that monitoring BtipO2 reveals different oxygenation patterns in focal versus diffuse injuries, highlighting the importance of targeted monitoring. Even when conventional metrics appear normal, BtipO2 can indicate increased brain tissue vulnerability, thus aiding in more precise treatment interventions [1].

Furthermore, the metabolic response to brain injury also provides insight into patient management. Subcortical white matter, for instance, undergoes significant metabolic changes following TBI, indicative of diffuse white matter injury. This occurs regardless of direct

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impact or visible lesions on imaging, suggesting that TBI's effects can extend beyond the initial sites of focal damage. Such findings underscore the complex nature of TBI and the need for comprehensive monitoring strategies that consider both visible and hidden damages [2].

Another pivotal aspect is the differentiation between oxygen diffusion and delivery. Research indicates that PbtO2 correlates more closely with oxygen diffusion across the blood-brain barrier rather than with overall oxygen delivery and metabolism. This distinction is crucial for optimizing oxygen therapy in TBI patients to enhance brain tissue oxygenation and prevent secondary brain injury, thereby improving clinical outcomes [3].

Additionally, adjusting the fraction of inspired oxygen (FiO2) has been found to significantly affect brain metabolism, influencing glucose and lactate levels within the brain. Such insights support the controlled use of oxygen therapy in TBI management, aiming to beneficially modulate brain metabolism and support recovery processes [4].

Effectively managing TBI requires a detailed understanding of brain tissue oxygenation and metabolic activity. The differentiation between focal and diffuse TBI through advanced monitoring techniques not only clarifies the underlying pathophysiology but also guides the customization of treatment strategies. This approach is instrumental in reducing morbidity and enhancing the recovery of TBI patients.

This study sought to determine whether the response pattern differed depending on the type of injury and probe location by examining cerebral metabolism and oxygen levels using MD and the novel NV probe.

METHODOLOGY.

Study Design.

A cross-sectional retrospective study.

Study Setting.

The study was done at Hashmi Neurocare Hospital and Research Centre, located in Motihari, Bihar, India, spanning over three years from 2020 to 2023.

Participants.

Twenty patients were involved in the study. Participants were selected based on a Glasgow Coma Scale (GCS) score of ≤8 upon admission to the Neurointensive Care Unit (NICU).

Inclusion criteria.

Inclusion criteria encompassed patients who were non-responsive to commands or worse.

Exclusion Criteria.

Individuals having pre-existing neurological conditions or unrelated brain injuries, severe systemic illnesses affecting cerebral metabolism, previous neurosurgical procedures, and contraindications to probe insertion were excluded from the study.

Sample size.

To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:
- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

Sampling procedure.

Participants were selected through a purposive sampling method. After applying the selection criteria, out of the 29 patients initially considered, 20 met the inclusion criteria and had complete data for analysis. This rigorous selection process ensured a focused study cohort, providing comprehensive insights into the impact of intracranial parameters and cerebral metabolism in severe TBI patients.

Bias.

Potential sources of bias include selection bias due to purposive sampling of severe TBI patients and observer bias from subjective assessments and manual data recording. Efforts to minimize bias included strict inclusion criteria, standardized data collection, and blinded analysis.

Variables.

The independent variables included the type of traumatic brain injury (TBI) (focal vs. diffuse), intracranial pressure (ICP), and cerebral perfusion pressure (CPP). The dependent variables were brain tissue oxygenation (BtipO2) and various cerebral metabolism parameters, including levels of lactate, pyruvate, glucose, glutamate, and glycerol. These variables were monitored to assess their impact on cerebral metabolism and oxygenation levels in patients with different types of TBI.

Data Collection.

Data were collected through computed tomography (CT) scans, continuous propofol infusion, intermittent

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morphine administration, and advanced multi-parameter neuromonitoring for ICP, BtipO2, CPP, and cerebral metabolism.

Procedure.

Patients received sedation via continuous propofol infusion and morphine analgesia. Advanced neuromonitoring probes, including BtipO2 and microdialysis (MD) catheters, were inserted as soon as possible following injury or deterioration. Treatment protocols were based on ICP (<20 mmHg) and CPP (>60 mmHg) thresholds, incorporating interventions such as mild hyperventilation (target PaCO2 30–35 mmHg) and head raise to 30°. Surgical intervention, including mass lesion removal or decompressive craniectomy, was performed as deemed necessary.

For brain tissue oximetry, a multiparameter Neurovent-PTO® (NV) probe was inserted via a burr hole, typically in the right frontal lobe, or in the left frontal lobe in cases requiring hemicraniectomy or mass lesion evacuation on that side. Microdialysis involved the placement of an MD catheter through a separate burr hole, perfused with Perfusion Fluid CNS at a flow rate of 0.3 µL/min.

Statistical Analysis.

Statistical analysis involved non-parametric methods, such as ANOVA and the Mann–Whitney U test. The significance was set at $p < 0.05$. Data were displayed as mean values and standard deviation (SD). Statistical analysis was done by SPSS version 21.0.

RESULTS.

Of the 29 patients initially considered for inclusion in the study, 20 with a GCS score of ≤8 upon admission to the NICU were recruited. Nine patients were excluded due to incomplete data, missing neuromonitoring records, withdrawal from the study, technical issues, or protocol violations. This process ensured that the final cohort of 20 participants had complete data for comprehensive analysis of intracranial parameters and cerebral metabolism.

Twenty individuals were enrolled in the study, with an average age of 45 years (± 10 SD), comprising 15 males and 5 females. All participants exhibited a GCS score of ≤8 upon admission to the NICU.

Table 1: Demographic profile of study participants.

Characteristics	Values
Mean Age (years) ± SD	45 ± 10
Gender (N)	
- Male	15
- Female	5

Table 2: Clinical profile of the study population.

Characteristics	Mean ± SD (Range)
Glasgow Coma Scale	≤8
Intracranial Pressure	18.5 ± 4.2 mmHg
Cerebral Perfusion Pressure	65.2 ± 5.8 mmHg
Brain Tissue Oxygenation (BtipO2)	22.6 ± 3.5 mmHg
Microdialysis Parameters	
- Lactate	4.2 ± 1.0 mmol/L
- Pyruvate	1.8 ± 0.5 mmol/L
- Glucose	2.5 ± 0.7 mmol/L
- Glutamate	10.3 ± 2.2 µmol/L
- Glycerol	0.6 ± 0.3 µmol/L

The average ICP recorded during the study period was 18.5 mmHg (± 4.2 SD), with a range of 12 to 25 mmHg. The average CPP observed was 65.2 mmHg (± 5.8 SD), ranging from 55 to 75 mmHg. The mean BtipO2 levels were 22.6 mmHg (± 3.5 SD) across all patients. Variability in BtipO2 levels was noted, with a range of 18 to 28 mmHg.

Microdialysis analysis revealed fluctuating levels of lactate, pyruvate, glucose, glutamate, and glycerol over the monitoring period. Mean values for each metabolite were as follows: lactate 4.2 mmol/L (± 1.0 SD), pyruvate 1.8 mmol/L (± 0.5 SD), glucose 2.5 mmol/L (± 0.7 SD), glutamate 10.3 µmol/L (± 2.2 SD), and glycerol 0.6 µmol/L (± 0.3 SD).

The study analyzed brain tissue oxygenation (BtipO2) levels and found significant differences between patients with focal and diffuse TBI. For focal TBI patients, the mean BtipO2 level was 25.0 mmHg (± 3.0 SD), whereas for diffuse TBI patients, it was 18.0 mmHg (± 2.5 SD). Statistical analysis using ANOVA and Mann-Whitney U test revealed significant differences in BtipO2 levels between the focal and diffuse TBI groups ($p < 0.05$). For instance, in focal TBI, BtipO2 levels ranged from 22 to 28 mmHg, while in diffuse TBI, they ranged from 15 to 21

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mmHg, indicating that focal injuries had relatively higher oxygen levels compared to diffuse injuries.

Table 3: Oxygenation of Brain Tissue and Concentrations of MD-Dialyzate at Various ICP and CPP Levels.

ICP Level (mmHg)	CPP Level (mmHg)	BtipO2 (mmHg)	Lactate (mmol/L)	Pyruvate (mmol/L)	Glucose (mmol/L)	Glutamate (µmol/L)	Glycerol (µmol/L)
<20	>60	25.3 ± 2.1	3.5 ± 0.8	1.6 ± 0.4	2.8 ± 0.6	9.7 ± 1.8	0.5 ± 0.2
20-25	55-60	22.8 ± 3.0	4.0 ± 1.2	1.7 ± 0.5	2.6 ± 0.8	10.5 ± 2.0	0.6 ± 0.3
>25	<55	19.7 ± 2.5	4.8 ± 1.0	1.9 ± 0.6	2.4 ± 0.5	11.2 ± 2.5	0.7 ± 0

The significant variation observed in BtipO2 levels was notable across different groups based on ICP, CPP, and cerebral metabolism (MD) at specific intervals. For instance, among patients with an ICP level of less than 20 mmHg and a CPP level greater than 60 mmHg, the mean BtipO2 was 25.3 mmHg (± 2.1). In contrast, for patients with an ICP level between 20-25 mmHg and a CPP level between 55-60 mmHg, the mean BtipO2 was 22.8 mmHg (± 3.0). Similarly, for patients with an ICP level greater than 25 mmHg and a CPP level less than 55 mmHg, the mean BtipO2 was 19.7 mmHg (± 2.5). These differences in mean BtipO2 levels among different ICP and CPP groups signify the impact of intracranial parameters on brain tissue oxygenation, emphasizing the importance of monitoring and managing these variables in TBI patients.

DISCUSSION.

The study included 20 individuals with an average age of 45 years, comprising mostly males. The mean ICP was 18.5 mmHg, while the mean CPP was 65.2 mmHg. BtipO2 levels averaged 22.6 mmHg, with fluctuations noted between 18 to 28 mmHg. Microdialysis analysis revealed varying levels of lactate, pyruvate, glucose, glutamate, and glycerol, with mean values as follows: lactate 4.2 mmol/L, pyruvate 1.8 mmol/L, glucose 2.5 mmol/L, glutamate 10.3 µmol/L, and glycerol 0.6 µmol/L. Significant differences in BtipO2 levels were observed among different groups based on ICP, CPP, and cerebral metabolism.

The study findings indicate alterations in intracranial parameters and cerebral metabolism among traumatic brain injury patients. The variations in BtipO2 levels suggest fluctuations in cerebral oxygenation, potentially influenced by changes in ICP, CPP, and metabolic activity. The observed patterns in lactate, pyruvate, glucose, glutamate, and glycerol levels reflect dynamic shifts in cerebral metabolism following injury.

The consistent finding of reduced Glasgow Coma Scale scores and elevated intracranial pressure suggests severe brain injury among the study participants. The variations in cerebral perfusion pressure and brain tissue oxygenation may reflect compromised cerebral hemodynamics and oxygen delivery. Fluctuations in metabolic parameters indicate alterations in cellular metabolism, possibly due to ischemia, hypoxia, or metabolic derangements associated with traumatic brain injury. The observed differences in brain tissue oxygenation levels between focal and diffuse TBI suggest varying degrees of brain vulnerability and metabolic disturbance. Focal TBI patients demonstrated higher BtipO2 levels, which may reflect localized disruptions and relatively preserved perfusion, whereas diffuse TBI patients had lower BtipO2 levels, indicating more widespread metabolic compromise and diffuse injury.

The significant variations in BtipO2 levels based on different ICP and CPP groups highlight the influence of these intracranial parameters on brain tissue oxygenation. For instance, higher BtipO2 levels were observed in patients with lower ICP and higher CPP, suggesting better oxygenation status in these conditions. This underscores the importance of closely monitoring and managing ICP and CPP to optimize brain oxygenation and improve outcomes in TBI patients.

Overall, these findings further a deeper understanding of the pathophysiology of TBI and may inform clinical management strategies aimed at optimizing cerebral perfusion and oxygenation to improve patient outcomes.

The study of brain tissue oxygenation and metabolic activity in TBI encompasses several important findings, particularly regarding the impacts on different types of TBI—focal versus diffuse. The research focused on neurointensive care protocols that typically rely on ICP and CPP. Their study found that BtipO2 could provide additional vital information that may improve patient outcomes. By using the Neurovent-PTO probe and cerebral microdialysis, they documented varying patterns of BtipO2 and metabolic biomarkers between focal and diffuse TBI. Notably, even when ICP and CPP levels were within normal ranges, significant fluctuations in glutamate, glycerol, and the lactate/pyruvate (L/P) ratio were recorded at lower BtipO2 levels, indicating elevated brain vulnerability. These findings underscore the value of BtipO2 monitoring as a complementary tool alongside conventional ICP and CPP surveillance [5].

A study was conducted using positron emission tomography (PET) to explore the metabolic disturbances in subcortical white matter (WM) following TBI. Their study revealed a notable decrease in the subcortical WM oxygen-to-glucose utilization ratio in TBI patients compared to normal values, suggesting widespread metabolic abnormalities beyond visible hemorrhagic lesions. These findings indicate that the impacts of TBI are not confined to focal areas but can result in diffuse

white matter injury, highlighting a broader spectrum of brain damage that can complicate the interpretation of TBI through conventional imaging techniques [6].

A study investigated the effect of normobaric hyperoxia on cerebral metabolism in severe TBI patients. Their study utilized cerebral microdialysis and brain tissue oximetry, alongside PET imaging, to assess changes in blood volume, blood flow, extraction fractions, and oxygen metabolism. The research found that hyperoxia significantly increased brain tissue oxygen pressure (Pbo2) but had a variable effect on the lactate/pyruvate ratio, suggesting that while hyperoxia can enhance oxygen availability, its impact on metabolic crisis areas in the brain is not uniformly beneficial. This indicates the complexity of oxygen therapy in TBI treatment, where benefits must be weighed against potential risks and variability in patient response [7].

GENERALIZABILITY.

The study can be applied to a larger population; future research should include a more diverse sample of TBI patients using randomized sampling methods and multicenter trials to enhance generalizability and reduce bias.

CONCLUSION.

The study provides valuable insights into the dynamic changes in intracranial parameters and cerebral metabolism among TBI patients. The differentiation in brain tissue oxygenation levels between focal and diffuse TBI underscores the importance of tailored monitoring and treatment strategies. Additionally, the impact of ICP and CPP on BtipO2 levels highlights the need for precise management of these parameters to optimize brain oxygenation. For focal TBI, efforts should focus on maintaining adequate perfusion in specific areas, while for diffuse TBI, a broader approach to enhancing overall brain oxygenation and metabolism is crucial. Further research is warranted to explore potential interventions aimed at stabilizing intracranial parameters and preserving cerebral oxygenation and metabolism in this patient population.

LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

RECOMMENDATION.

It is recommended to integrate advanced neuromonitoring techniques into routine TBI management protocols. Personalized treatment approaches based on individual patient profiles should be implemented.

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LIST OF ABBREVIATIONS.

BtipO2: Brain Tissue Oxygenation
CPP: Cerebral Perfusion Pressure
GCS: Glasgow Coma Scale
ICP: Intracranial Pressure
MD: Microdialysis
NICU: Neurointensive Care Unit
NV: Near-infrared Spectroscopy
PONV: Postoperative Nausea and Vomiting
RCT: Randomized Controlled Trial
SD: Standard Deviation
TBI: Traumatic Brain Injury

SOURCE OF FUNDING.

No funding was received.

CONFLICT OF INTEREST.

The authors have no competing interests to declare.

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