ORIGINAL ARTICLE
Indonesia Surgical Journal (*INASJ*) 2024, Volume 1, Number 2 : 22-30

Relationship of Hyperbaric Oxygen Therapy with Glasgow Coma Scale (GCS) Dynamics in Traumatic Brain Injury Patients

Garry Grimaldy[1*], Eko Prasetyo[2], Yovanka Naryai Manuhutu[2], F. L. Fredrik G. Langi[3]

[1]Department of Surgery, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia;
[2]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia;
[3]School of Public Health, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia.

*Corresponding author:
Garry Grimaldy;
MD. Department of Surgery, School of Medicine, University of Sam Ratulangi, Manado, Indonesia;
garrygrimaldy@hotmail.com

Received: 2024-08-07
Accepted: 2024-10-05
Published: 2024-11-15

ABSTRACT

Background: Traumatic brain injury (TBI) is one of the diseases that cause morbidity and mortality in 69 million people each year. The severity of brain injury is categorized and measured according to Glasgow Coma Scale (GCS) scoring. Hyperbaric oxygen therapy (HBOT) is a therapeutic alternative that can influence the patient's level of consciousness through intracellular mechanisms. This study aims to identify the relationship of HBOT to the GCS dynamics in TBI patients.
Methods: Meta-analysis was conducted on randomized controlled trial studies of patients diagnosed with TBI using GCS measurement. Literature searches were performed on several databases, namely Pubmed, Scopus, and Cochrane Library. Risk of bias analysis was carried out using the ROB2 tool. Other data analysis, including treatment effect measurement, heterogeneity, forest plot, and funnel plot, were analyzed in R-studio. Standardized mean difference (SMD) was calculated using a 95% confidence interval.
Result: Meta-analysis of four studies showed high heterogeneity in the I^2 test, which was 92.8% [84.7%; 96.6%] and τ^2 test, which was 1.458 [0.391; 21.828]. Forest plot analysis demonstrated a significant difference in GCS between the control and intervention groups. The pooled effect favored the HBOT intervention group with SMD = 1.80 and CI 95% = 0.58; 3.03. Publication bias analysis visualized in the funnel plot resulted in scattered data in the outer area of the funnel, indicating a low study size involved in this analysis.
Conclusion: The outcome of the meta-analysis indicated the significance of hyperbaric oxygen therapy (HBOT) intervention in improving patients' consciousness measured in the Glasgow Coma Scale (GCS), compared to the control group with standard care.

Keywords: traumatic brain injury, Glasgow Coma Scale, hyperbaric oxygen therapy, meta-analysis.
Cite This Article: Grimaldy, G., Prasetyo, E., Manuhutu, Y.N., Langi, F.L.F.G. 2024. Relationship of Hyperbaric Oxygen Therapy with Glasgow Coma Scale (GCS) Dynamics in Traumatic Brain Injury Patients. *Indonesia Surgical Journal* 1(2): 22-30

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common diseases causing morbidity and mortality in the world.[1] It affects 69 million people each year, with the main causes of injury being traffic accidents, falls from height, and violence.[2] Southeast Asia is the most affected region, with Indonesia having the fourth highest incidence globally.[3]

Head injuries are divided into three categories, which are mild brain injury, moderate brain injury, and severe brain injury, as measured by the Glasgow Coma Scale (GCS).[4,5] The mechanism of brain injury is divided into three main stag: primary brain injury, secondary brain injury and tertiary brain injury. Primary brain injury begins when the patient experiences an impact that results in mechanical damage, such as damage to the blood-brain barrier in the brain. The damage to brain tissue will become more and more destructive over time, initiating a cascade of inflammatory signaling in the affected area. This process is referred to as secondary brain injury, where the damage has penetrated the immune system and tissues. The highest damage occurs in tertiary brain injury characterized by brain nerve cell death (neurodegeneration).[6–8]

Hyperbaric oxygen therapy (HBOT) is a therapeutic approach that utilizes exposure to pure oxygen (O2) at a specific atmospheric pressure[9]. Damage caused by brain injury creates a hyperoxic state that can increase the transcriptional and translational activity of proinflammatory cytokines (19-23 Beynon). Hyperbaric oxygen therapy is performed with maximum oxygen concentration (100%) at a higher pressure than normal pressure to maximize oxygen supply in the blood.[10]

Brain injury is closely related to the patient's level of consciousness. Considering this fact, measuring the dynamics of the Glasgow Coma Scale score can be a reference for the effectiveness of therapy. This meta-analysis was conducted as a pioneering study of the development of HBOT on GCS scoring dynamics that are representative of patient recovery responses.

METHODS

Research Design

Writing systematic review and meta-analysis protocols refers to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and the PRISMA-NMA extension.

Inclusion Criteria

This study only considered studies in the form of trials with control groups, such as randomized controlled trials or controlled clinical trials. Quasi-experiments (placebo), review articles, expert opinions, case reports, and case series were excluded from the analysis.

Study selection was conducted within the PICO framework:

1) Population: Traumatic brain injury (TBI) patients.
2) Intervention: Hyperbaric oxygen therapy (HBOT)
3) Comparison: TBI treatment without HBOT intervention
4) Outcome: Glasgow Coma Scale (GCS) score.

Data Source

A literature search was conducted in several electronic databases, including the Cochrane Central Register of Controlled Trials, MEDLINE (via PubMed) and Scopus. All English-language trials that met the inclusion criteria were included, with no restriction on the year of publication.

Search Strategy

Literature search using Pubmed, Scopus, and Cochrane Library was conducted specifically using medical subject headings (MeSH) keyword search with search builder: ((“Hyperbaric Oxygenation”[Mesh]) AND “Brain Injuries, Traumatic”[Mesh] AND “Humans”[Mesh])). The literature obtained through the electronic search was imported into the Mendeley Library for literature checking, including eliminating duplicate data. Two researchers performed study eligibility selection with reference to the inclusion criteria.

Data Collection and Analysis

Information collected from each study included publication data (title, author, year of publication, etc. as relevant), participant characteristics (age, sex, etc. as available), intervention details (treatment of experimental and control groups respectively, frequency, intensity, duration, follow-up), outcome and outcome measurement instruments, study design (randomization, blinding), adverse events, and other information for analysis.

Evaluation of the quality and risk of bias in the selected studies was carried out by two researchers independently according to the Cochrane risk of bias assessment guidelines using the RoB 2 tool (revised tool for Risk of Bias in randomized trials). The evaluation results were expressed as a risk of bias graph and a risk of bias summary.

The parameters reviewed in this study were continuous variables calculated as standard mean difference (SMD) with 95% confidence interval (CI). Statistical significance was defined as a p-value <0.05.

The selected studies’ statistical heterogeneity was assessed using the I^2 statistic and the chi-square test. An I^2 value of >75% or a chi-square test result with $p < 0.1$ was the benchmark for consideration of high heterogeneity among the selected studies. Analyses of studies with evidence of heterogeneity were conducted using the random-effects model, and conversely, if there was no indication of heterogeneity, the calculation used the fixed-effects model.

Data analysis and plot synthesis were performed using R software and R Studio. Under conditions of low statistical heterogeneity, the meta-analysis was conducted using the fixed-effects model. Meanwhile, in the case of high heterogeneity, pooled-effects estimation analyses were conducted using the random-effects model.

The analysis of potential reporting bias was depicted in a funnel plot to see visual asymmetry. Another asymmetric test, the Egger test, could not be performed on the outcomes due to the small number of studies compared (<10 studies).

Variable Operational Definition

The following are the variables measured in this study:

RESULT

Study Selection

The initial study search was conducted using a specific search builder that included each of the defining terms of the study variables, namely Interleukin-1, Interleukin-6, Interleukin-10, Matrix Metallo-proteinase-9, and Glasgow Coma Scale. A search using this method did not yield any meaningful data. The lack of search results indicates a lack of publications that discuss the research target as the main topic.

Because of this, a search was conducted without entering specific variable definition terms using a search builder (“Hyperbaric Oxygenation”[Mesh]) AND “Brain Injuries, Traumatic”[Mesh] AND “Humans”[Mesh]) and 397 studies were obtained from three database websites, namely PubMed, Scopus, and Cochrane Library. The study selection is illustrated in the following diagram.

Study Characteristics

Research type and year

Four journals were selected as randomized controlled trials published in English. The four journals were included in the inclusion criteria based on the Glasgow Coma Scale measurement variable after hyperbaric oxygen therapy treatment.

Table 1. Variables and operational definitions

Variables	Operational Definition	Scale
	Dependent Variable	
GCS	Clinical scale used to assess consciousness based on eye, verbal, and motor assessments as described	Numeric
	Independent Variable	
HBOT	TBI patient intervention: added HBOT and without HBOT	Categoric
TBI	Total Glasgow Coma Scale score, categorized by: mild (score 13-15), moderate (score 9-12), and severe (≤8)	Categoric

Participant

The studies included in this meta-analysis involved 246 participants with a range of ages. The participants involved in the study had a history of traumatic brain injury with a classification of moderate to severe brain injury based on GCS scores measured at the start of the study (baseline). The study was dominated by participants with severe levels of injury, with GCS scores of 3-8.

Intervention

This analysis performs hyperbaric oxygen therapy with maximum oxygen levels of 99.5-100% using either monochamber or multi-chamber therapy chambers. Differences exist in the pressure used and the duration of oxygen exposure to patients.

In this analysis, there is a gap in the frequency of therapy in the Prakash et al. study, which is 3 times with a duration of 1 week, relatively shorter than other studies. The authors did not include any information regarding the concept of the method applied, but this may correlate with the age of the participants, who were children aged 5-12 years.

Outcome

In this case, the outcome reviewed is the Glasgow Coma Scale, consisting of a range of 0-15, representing the patient's level of consciousness, with each parameter having a maximum measurement scale of 4, 5, and 6, respectively. Based on the study of Gennarelli et al.,[11] GCS scores have a progressive correlation that continually increases patient mortality after head injury. The severity of the injury can be classified into three levels, namely severe TBI (GCS 3-8), moderate TBI (GCS 9-12), and mild TBI (GCS 13-15).

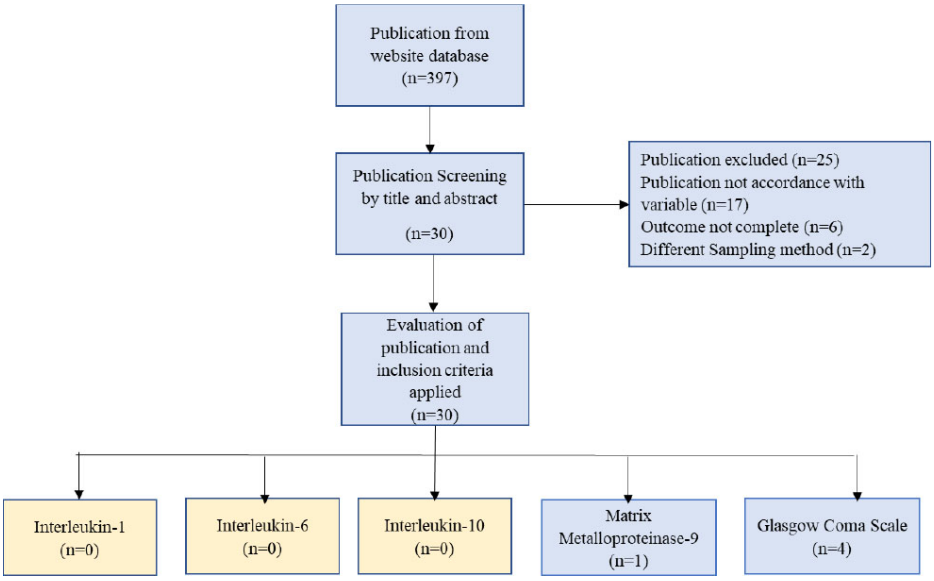

Figure 1. Study selection flowchart.

Risk of Bias Between Studies

RoB 2 consists of five main domains that contain a series of related questions. The assessment is highly subjective, requiring more than one observer to increase the robustness of the assessment results. The risk of bias assessment was conducted independently by two observers, DV and GG.

Based on the risk of bias analysis of the studies conducted, the study of Liu et al. (ID: GCS_02) and Zhong et al. (ID: GCS_04) had a low risk in all reviewed domains. In contrast, Lin et al. (ID: GCS_01) and the study of Prakash et al. (ID: GCS_03) had a noteworthy risk of study bias (Figures 2 and 3). These studies were still included in the analysis

Table 2. Year, type, and research variables

Study Source	Year	Type	Variable
Lin et al., 2008 [101]	2004-2005	Randomized controlled trials	GCS
Liu et al., 2022 [102]	2020-2021	Randomized controlled trials	GCS
Prakash et al., 2012[103]	2012	Randomized controlled trials	GCS
Zhong et al., 2020[104]	2016-2018	Randomized controlled trials	GCS

Table 3. Characteristics of participants

Study Source	Age (year)	Participant			Baseline	
		Intervention	Control	Total	GCS	Classification
Lin et al., 2008	24-65	22	22	44	3-12	Moderate-Severe
Liu et al., 2022	N/A	29	29	58	3-8	Severe
Prakash et al., 2012	5-12	28	28	56	<8	Severe
Zhong et al., 2020	37-53	44	44	88	3-8	Severe

Table 4. Characteristics of the study intervention

Study	Intervention			Control		
	Participant	Mean GCS	Deviation	Participant	Mean GCS	Deviation
Lin et al., 2008	22	13.5	2.50	22	11.5	5.10
Liu et al., 2022	29	11.28	1.63	29	7.25	1.14
Prakash et al., 2012	28	14	0.82	28	10	1.69
Zhong et al., 2020	44	12.06	2.76	44	9.16	2.84

Table 5. Study outcome characteristics with oxygen therapy

Study Source	Oxygen Saturation	Pressure	Surgery duration	Therapy	Frequency	Therapy Duration
Lin et al., 2008 [101]	100%	2 ATA	90-120 min	Multi-user pressurized chamber	20 times repetition	4 weeks
Liu et al., 2022 [102]	99.5%	1.8 – 2.2 ATA	60-80 min	Chamber with 3 compartment and 7 doors	20 times repetition	4 weeks
Prakash et al., 2012 [103]	100%	2-3 ATA	90-120 min	Monoplace chamber	3 times repetition	1 week
Zhong et al., 2020 [104]	100%	2 – 2.5 ATA	120 min	chamber	14 times repetition	2 weeks

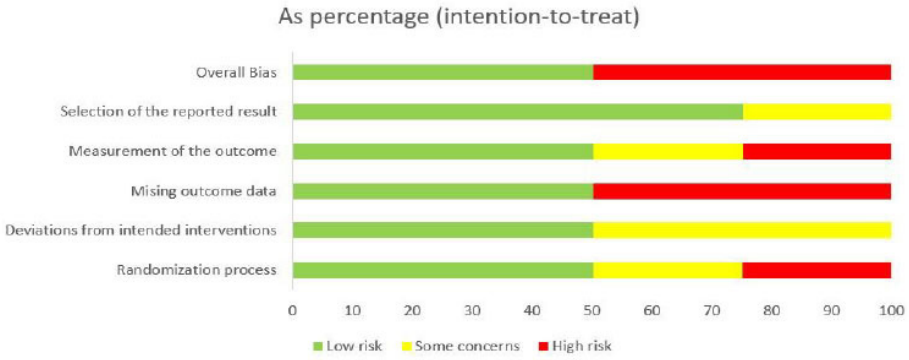

Figure 2. Risk of bias analysis results using ROB2.

Figure 3. Glasgow Coma Scale (GCS) risk of bias study chart

```
> df_smd

                Study NT MeanT  SDT NC MeanC  SDC      yi      vi
1     Lin et al., 2008 22 13.50 2.50 22 11.50 5.10 20.8468 13.3731
2     Liu et al., 2022 29 11.28 1.63 29  7.25 1.14 25.4337 39.5654
3 Prakash et al., 2012 28 14.00 0.82 28 10.00 1.69 25.7655 29.0862
4   Zhong et al., 2020 44 12.06 2.76 44  9.16 2.84 40.6008 69.1457
```

Figure 4. Calculation of effect size values and their variations.

considering the comprehensiveness of the substance, which could be an interesting point for meta-analysis studies related to the effectiveness of hyperbaric oxygen therapy in patients with traumatic brain injury, especially with GCS measurements that have not been done before.

Treatment Effect Measurement

A continuous variable was used in the GCS score analysis in the form of a standardised mean difference (SMD). SMD was calculated using the mean as well as the standard deviation. Individual data calculations were performed using R studio, with additional data results in the form of 'yi' and 'vi', showing the effect size and variation (Figure 4).

Heterogeneity and Determination Analysis of Cumulative Effect Model

The calculation of heterogeneity in this meta-analysis was carried out by several measurement methods, such as Cochran's Q, chi-square, $\tau^{2,}$ or I^2.

The I^2 heterogeneity test showed a high heterogeneity result of 92.8% [84.7%; 96.6%]. The same result was shown in the τ^2 heterogeneity test with a value of 1.458 [0.391; 21.828]. These heterogeneity test results indicate a very high heterogeneity in the total variation that cannot be explained by chance alone. Several factors, such as patient characteristics, study design, and differences in intervention methods, may influence the high heterogeneity. This analysis used a randomized model effect, considering the relatively small study size and the high heterogeneity due to the many factors affecting the outcomes.

Results of Data Synthesis (Forest Plot)

Glasgow Coma Scale variables were measured within the observation range (1-15) and classified as continuous variables. This analysis was conducted using standardized mean difference (SMD) to equalize differences in the severity of participants' brain injury between studies.

The use of standardized mean difference (SMD) affects the location of the no-effect line, which is at point 0. Studies with a confidence interval value regarding the no-effect line indicate a non-significant effect on the two groups being compared, the intervention group (performing hyperbaric oxygen therapy) and the control group. The confidence interval in the Lin et al. study[12] intersected the line of no effect, indicating a non-significant result in the intervention group (Figure 7). The cumulative effect (pooled effect) visualized in Figure 5.6.1 in the shape of a diamond revealed a significant result in favor of the intervention group, with an SMD of 1.80 and a 95% confidence interval of [0.58; 3.03].

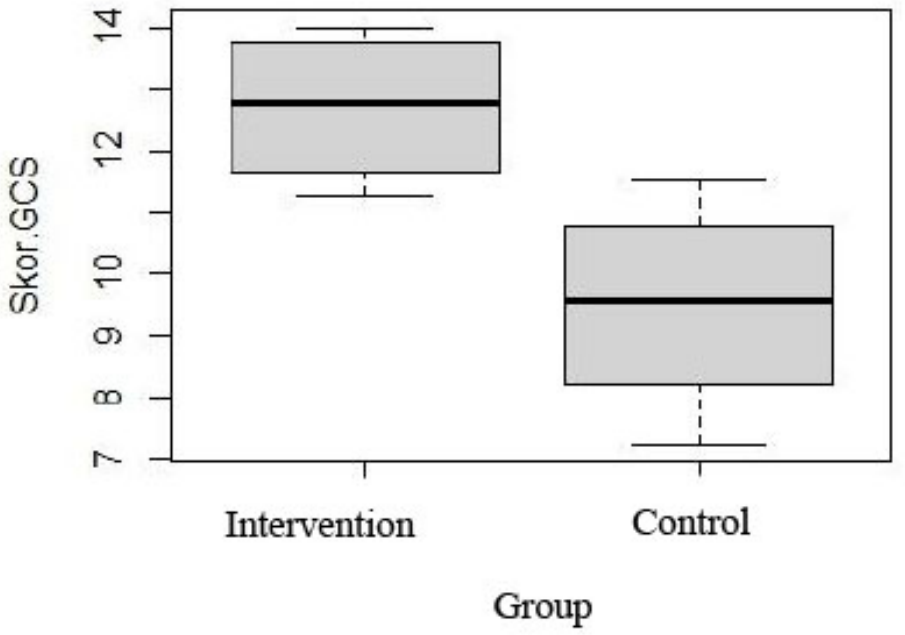

Figure 5. Boxplot of cumulative final results of GCS data.

```
Number of studies: k = 4
Number of observations: o = 246

                         SMD            95%-CI    z p-value
Random effects model 1.8035 [0.5764; 3.0306] 2.88  0.0040

Quantifying heterogeneity:
 tau^2 = 1.4580 [0.3913; 21.8285]; tau = 1.2075 [0.6255; 4.6721]
 I^2 = 92.8% [84.7%; 96.6%]; H = 3.71 [2.55; 5.40]

Test of heterogeneity:
     Q d.f.  p-value
 41.39    3 < 0.0001

Details on meta-analytical method:
- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Hedges' g (bias corrected standardised mean difference; using ex
act formulae)
```

Figure 6. Heterogeneity test results (I^2 and τ^2)

Publication Bias Analysis

The results of the analysis of potential publication bias show that the publications analyzed in this study have very diverse effect sizes, with not a single publication falling within the funnel. The publications have relatively high standard errors, judging by the location of the dots at the bottom, indicating the low size of the studies involved in this analysis.

DISCUSSION

Traumatic head injury or brain injury (TBI) is caused by external activities or physical attacks that impact the head and brain area. The severity of TBI can be classified based on Glasgow Coma Scale (GCS) scoring. On a global scale, mild TBI accounts for 81% of brain injuries, moderate TBI 11%, and severe TBI 8%. Traumatic brain injury is the leading cause of death and disability worldwide, accounting for approximately 30% of all injury deaths.

Hyperbaric oxygen therapy can be used as a support therapy in various inflammatory conditions such as soft tissue necrosis infections, gas gangrene, burns, chronic wounds, and refractory osteomyelitis. In several studies, HBOT has had positive results on the recovery of patient consciousness, as measured by an increase in the GCS scale.

Research Development and Selection of HBOT Studies in Patients with TBI

Meta-analysis begins with a search for studies according to the variables to be reviewed. However, searching for studies according to variables provides very minimal results due to the small number of publications available. Because of this, the search was carried out manually to see the research model for the effectiveness of HBOT in patients with TBI.

Based on the search data that has been carried out, monitoring the effectiveness of HBOT in patients with brain injury is measured using several methods: physical monitoring, psychological testing, questionnaires, radiographic imaging, and measurement of body fluid sample parameters. To date, research on the effectiveness of HBOT for TBI recovery is generally measured using cognitive assessment and radiographic imaging.

HBOT studies on proinflammatory cytokines have not been commonly conducted, resulting in limited publications. This is due to the ethical limitations of human studies and the difficulty of removing confounding factors that may contribute to data bias. Because of this, research on proinflammatory cytokines is generally conducted on animal subjects.

However, several studies discuss GCS values as a parameter for assessing patient consciousness. Most studies used GCS measurement as secondary data, so no meta-analysis discusses GCS as the main variable. Of the 10 studies that discussed GCS, there were only 4 studies that could be analyzed further according to the completeness of the data needed in statistical processing. Because of this, the meta-analysis conducted in this study is considered a pioneer in developing HBOT as a whole.

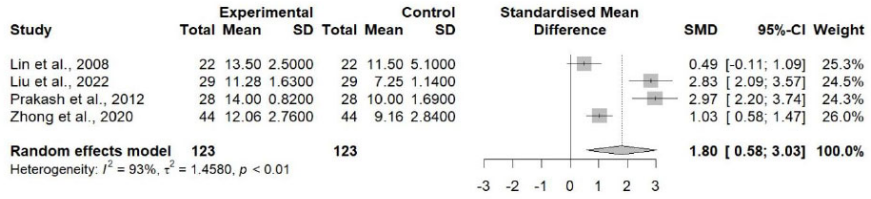

Figure 7. Results of forest plot analysis on GCS variables

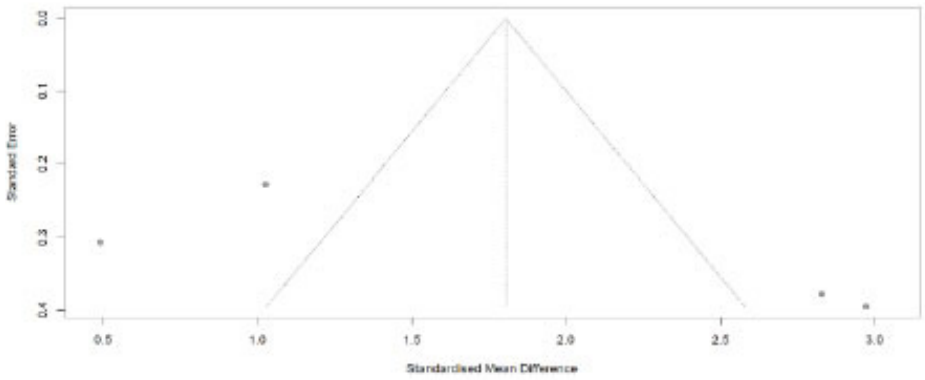

Figure 8. Results of funnel plot analysis.

Liu et al.[13] conducted a study on the effect of consciousness of traumatic brain injury patients on the combination of hyperbaric oxygen therapy and low-frequency repetitive transcranial magnetic stimulation (rTMS). rTMS is used to induce plasticity of the central nervous system and can be used as an adjuvant therapy for patients with epilepsy, spinal cord injury, psychosis, and cerebral infractions that are non-invasive. Liu et al. combined rTMS with HBOT, which is beneficial for brain injury patients. A total of 58 participants were randomly assigned to the control and intervention groups with initial GCS scores of 3-8. Changes in brain imaging were observed through CT scans and MRI. This study showed that the combination of rTMS with HBOT can significantly improve GCS and BAEP scores, judging from the comparison of the control group with the intervention group.

Lin et al.[12] conducted research from 2004 to 2006 with 44 participants who met the criteria. Participants were randomly divided into two groups (intervention and control). The HBOT intervention was given using a mask in a multi-user pressurized chamber for 2 hours with a pressure of 2 ATA. The pressure was increased slowly until it reached 2 ATA with 100% oxygen concentration. Overall, participants underwent HBOT 20 times in 4 weeks. This study was conducted to see changes in GCS scores, the severity of the injury, and the period of HBOT performed. The level of recovery of brain injury conditions is measured using the Glasgow Outcome Scale (GOS). This study showed a significant difference in GCS scores in the intervention group with an increase in GCS score of 2.4. Similar results were shown in the GOS score, with more changes in GOS scores found in the intervention group. However, the authors stated that there was a lack of data to conclude the results' significance.

Prakash et al.[14] focused on pediatric participants (5-12 years) with a history of traumatic brain injury. A total of 54 participants were randomly divided into two groups with similar initial state of consciousness (GCS < 8). HBOT inhalation was administered with 100% oxygen concentration in a monoplace chamber pressurized above 1 atmosphere (atm) for 90-120 minutes. Functional, social, and clinical parameters were observed throughout the study process. Participants in the intervention group tended to show positive changes, characterized by the development of social skills, decreased duration of hospitalization, reduction of disability to return to activities, and improved GCS scores. The intervention group significantly increased GCS scores during the first-week therapy interval. Overall, the administration of HBOT can improve patient's quality of life with TBI and reduce the risk of further complications.

The study of Zhong et al.[15] was conducted at Shenzhen People's Hospital (China) for approximately 30 months (2016-2018). This study involved 88 participants with a diagnosis of severe brain injury (GCS 3-8) who were randomly divided using the random number table method. HBOT was administered to the intervention group using a 0.20-0.25 MPa pressurized chamber, followed by increased pressure for the first 20 minutes, oxygen inhalation at a fixed pressure for 80 minutes, and decompression for 20 minutes. Both groups received therapy once/day for 2 weeks. Several variables were measured in this study, with GCS, NIHSS, and GOS scores taken before and after HBOT being secondary data. The study showed a comparison of metabolic values and cerebral blood flow in both groups improved significantly. However, the intervention group showed higher oxygen intake rate, Vs, and Vm with lower Pi and intracranial pressure values than the control group. The same pattern was shown in the final GCS and NIHSS scores, with the intervention group showing significant changes. In the intervention group, the GCS score increased from 6.18 ± 1.44 to 12.06 ± 2.76 NIHSS score decreased from 19.61 ± 2.19 to 8.46 ± 2.37. Overall, the study of Zhong et al. showed the positive effect of HBOT on brain injury recovery

Study Characteristics

In the literature review, all four GCS studies described showed a significant effect of HBOT in the intervention group. The studies involved randomly grouped participants to reduce bias factors that could affect the overall data. The time difference of the studies tends to show improvisation of measurement methods that are more collaborative and comprehensive. The study by Lin et

al.[12] is the oldest study compared with a relatively simple measurement complexity, comparing GOS and GCS values between research groups. Similarly, the study of Prakash et al.[14] with a relatively shorter and simpler study in terms of methods and discussion. Research by Zhong et al.[15] and Liu et al.[13] shows the complexity of measurements with new technologies, such as the measurement of brain metabolic variables and the combination of rTMS in HBOT interventions. The variation of study years can provide gradual information to improve the accuracy of guidelines to be developed in the future.

All four studies involved participants with severe TBI (GCS 3-8) with additional cases of moderate TBI (GCS 9-12) in the study of Lin et al.[12] Clinically, patients with a history of severe TBI have experienced a secondary injury phase, where inflammatory reactions are very likely to occur in this case. The ages of participants in these studies varied greatly, ranging from pediatric patients in the study of Prakash et al.[14] to elderly patients in other studies. GCS scoring can be used to evaluate consciousness in all age ranges, except in infants under 5 years old. The Paediatric Glasgow Coma Scale (PGCS) tests consciousness in children under 5 years old with modifications to verbal responses.[16] In the GCS variable, age was considered to have no effect on the resulting outcomes, so the study of Prakash et al.[14] could still be included in the analysis.

Although conducted in relatively different conditions in terms of chamber and inclusion characteristics, other intervention characteristics are in a similar range, such as oxygen levels (99.5% - 100%), pressure (1.8-3 ATA), and duration (60-120 minutes) with some studies being exceptions to certain characteristics. The repetition frequency is generally one to three times a day (90-120 minutes) with 20 to 60 repetitions depending on the patient's condition and disease.[17] As shown in Table 5.2.3, repetitions vary in the range of 14-20 times with the Prakash et al. study data as an outlayer. The low frequency of repetition in the Prakash et al. study needs to be explored further to ensure the reliability and comparability of the analysed data.

Risk of Bias Between Studies

A risk of bias analysis was conducted to assess the reliability of each study involved in the analysis. Based on the two-observer analysis results, no differences in results or disagreements were reported in the discrepancy check. The Liu et al. and Zhong et al. studies have a low risk of bias with complete information that suits the needs of the analysis. In contrast, the Lin et al. study and the Prakash et al. study had a lot of incomplete data, indicating a high risk of study bias that could affect further statistical analyses.

Based on the observation of the classification of issues,[18] the most prominent factor affecting the assessment of bias in the Lin et al. study and the Prakash et al. study was the incompleteness of the report and the lack of information included in the study. Internal validity testing requires adequate reporting of the study. Under certain conditions, observers may contact the study authors for additional information. In these cases, the observation becomes more focused on the incompleteness of the data rather than on the overall conduct of the study. This can be addressed using other testing tools that include an "unclear risk of bias" option for incomplete studies so that it is more representative of the overall study content.[18] Based on the quality considerations of internal validity, both studies were included in further analyses.

Discussion on treatment effects, heterogeneity, and statistical analysis

The heterogeneity analysis showed very high differences in the four studies compared. The high heterogeneity in the studies may be influenced by various factors, with the dominant factors in this analysis being differences in intervention methods, frequency of therapy, and patient characteristics. The study by Sabitova et al.[19] showed that analyses with a broad framework or prevalence of phenomena in diverse environments can produce highly heterogeneous studies. In this case, the characteristics of the participants in the inclusion criteria varied in terms of disease history, gender, and other clinical conditions. Similarly, the intervention methods and frequency of therapy varied greatly, resulting in high heterogeneity.

Despite the high heterogeneity, the final GCS results gave a similar pattern in each study, with the intervention group showing highly significant results with GCS values > 11. In contrast, the control group showed relatively mixed results. Because of this, analyses can be conducted using a random-effects model that places studies at almost equal weight regardless of sample size. This model can produce a meta-analysis summary close to the arithmetic mean which is simpler and more representative.[20]

The cumulative effect showed significant results in favor of the intervention group with an SMD value of 1.80 and a 95% confidence interval of [0.58; 3.03]. The cumulative confidence interval is relatively wide, indicating low precision due to relatively scattered data. Almost all studies showed significant results, except the Lin et al. study with an IK-95% crossing the line of no effect. This could be due to the high standard deviation of GCS scores in both the control and intervention groups. In their study, Lin et al. stated that the significance of the average GCS score in the control group (p-value <0.05) means the distribution is very diverse and scattered. The other three studies showed significance in the intervention group, with the most precise 95% CI interval in the Zhong et al. study. Participants in the intervention group showed development of consciousness in the form of increasing GCS values and categories, namely severe traumatic brain injury (GCS 3-8) to mild traumatic brain injury (GCS>8). The results of the forest plot analysis illustrated a significant change in GCS values in participants who had hyperbaric oxygen therapy compared to participants who were only treated with standard control.

The results of this analysis show the significance of recovery after HBOT and several other studies on brain injury participants with various research variables. The series of studies by Rockswold et al.[21–24] showed significant improvement in measuring brain metabolism variables, blood oxygen concentration, and intracranial pressure. Another series of studies, namely that of Harch et al.[25–27] showed a reduction in symptoms such as headaches as well as an improvement in patients' quality of life as measured by

various cognitive tests. The restorative effect of HBOT was also observed on single photon emission computed tomography (SPECT) radiographic imaging with bilateral heterogeneous frontal and temporal defects recovering after HBOT was administered. The study of Hadanny et al.[28] showed similar results in measuring a series of cognitive tests and brain imaging using SPECT. In this study, the authors stated that HBOT also affects brain neuroplasticity and there is a strong correlation between specific cognitive functions and brain metabolism recovery illustrated in SPECT results. These results are relatively consistent in many studies, indicating the effectiveness of HBOT as an adjuvant therapy in brain injury recovery.

The meta-analysis conducted in this study is novel, pioneering the development of the effectiveness of HBOT in patients with TBI by measuring neuroinflammatory biomarker variables and GCS scoring. Because of this, several limitations could potentially affect the overall reliability of the analysis. Firstly, the number of studies was relatively limited, with the number of publications <10. The more studies compared, the more variations in data that illustrate the holistic effects of hyperbaric oxygen therapy (HBOT) on traumatic brain injury (TBI) patients. Secondly, the studies involved in the analysis were conducted with a small participant population and a wide range of interventions. This may affect the outcome values and statistical analyses. Analyses in small populations are considered more sensitive to drift and thus have a relatively large potential for bias. Third, variations in study design, interventions, and participant characteristics are the main reasons for the high heterogeneity of the studies. The funnel plot visualization depicted highly scattered data in the area outside the funnel, illustrating a high degree of error in all compared studies.

CONCLUSION

Based on the analysis that has been done, it can be concluded that hyperbaric oxygen therapy (HBOT) provides significant changes in consciousness in patients with traumatic brain injury (TBI) as measured by the dynamics of increasing GCS scores.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest regarding this article.

ETHICS APPROVAL

Not Applied.

FUNDING

This study was self-funded.

AUTHOR CONTRIBUTION

All authors contributed equally.

REFERENCE

1. Tandean S, Japardi J, Kollins F, Loe ML (2020) Epidemiology of traumatic brain injury in neurosurgery department of tertiary referral hospital at North Sumatera, Indonesia. Medicinus 7:146
2. Dewan MC, Rattani A, Gupta S, et al (2018) Estimating the global incidence of traumatic brain injury. J Neurosurg 130:1080–1097
3. World Bank (2022) Indonesia Overview: Development news, research, data. In: https://www.worldbank.org/en/country/indonesia/overview.
4. Niryana IW, Junior IWJ, Darmawan R, Widyadharma IPE (2020) Characteristics of traumatic brain injury in sanglah hospital, Bali, Indonesia: A retrospective study. Biomed Pharmacol J 13:1431–1437
5. Rosyidi RM, Priyanto B, Laraswati NKP, Islam AA, Hatta M, Bukhari A, Kamil M, Wardhana DPW (2019) Characteristics and clinical outcome of traumatic brain injury in Lombok, Indonesia. Interdisciplinary Neurosurgery 18:100470
6. Pardamean DT, Prasetyo E, Oley M (2015) Therapeutic mild hypothermia towards blood lactate levels and Glasgow coma score in severe traumatic brain injury. Bali Med J 4:82
7. Prasetyo E (2020) The primary, secondary, and tertiary brain injury. Crit Care Shock 23:4–13
8. Wu M-Y, Gao F, Yang X-M, Qin X, Chen G-Z, Li D, Dang B-Q, Chen G (2020) Matrix metalloproteinase-9 regulates the blood brain barrier via the hedgehog pathway in a rat model of traumatic brain injury. Brain Res 1727:146553
9. Oley MH, Oley MC, Kepel BJ, Faruk M, Wagiu AMJ, Sukarno I, Tulong MT, Sukarno V (2024) Hyperbaric Oxygen Therapy for Diabetic Foot Ulcers Based on Wagner Grading: A Systematic Review and Meta-analysis. Plast Reconstr Surg Glob Open 12:e5692
10. Ortega MA, Fraile-Martinez O, García-Montero C, et al (2021) A general overview on the hyperbaric oxygen therapy: Applications, mechanisms and translational opportunities. Medicina (Kaunas) 57:864
11. Gennarelli TA, Champion HR, Copes WS, Sacco WJ (1994) Comparison of mortality, morbidity, and severity of 59,713 head injured patients with 114,447 patients with extracranial injuries. J Trauma 37:962–968
12. Lin JW, Tsai JT, Lee LM, et al (2008) Effect of hyperbaric oxygen on patients with traumatic brain injury. In: Chiu W-T, Chiang Y-H, Kao M-C, Hung C-C, Lin S-Z, Chen H-J, Tang SFT, Hoffer BJ (eds) Reconstructive Neurosurgery. Springer Vienna, Vienna, pp 145–149
13. Liu M, Li Q, Bao Y, Ma Y, Niu Y, Zhang F (2022) [Retracted] Effect of Low Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Combined with Hyperbaric Oxygen (HBO) on Awakening of Coma Patients with Traumatic Brain Injury. J Healthc Eng 2022:6133626
14. Prakash A, Parelkar S V, Oak SN, Gupta RK, Sanghvi B V, Bachani M, Patil R (2012) Role of hyperbaric oxygen therapy in severe head injury in children. J Pediatr Neurosci 7:
15. Zhong X, Shan A, Xu J, Liang J, Long Y, Du B (2020) RETRACTED: Hyperbaric oxygen for severe traumatic brain injury: a randomized trial. Journal of International Medical Research 48:0300060520939824
16. Borgialli DA, Mahajan P, Hoyle Jr. JD, et al (2016) Performance of the Pediatric Glasgow Coma Scale Score in the Evaluation of Children With Blunt Head Trauma. Academic Emergency Medicine 23:878–884
17. Lam G, Fontaine R, Ross FL, Chiu ES (2017) Hyperbaric Oxygen Therapy: Exploring the Clinical Evidence. Adv Skin Wound Care 30:
18. Viswanathan M, Ansari MT, Berkman ND, et al (2012) Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Agency for Healthcare Research and Quality .
19. Sabitova A, McGranahan R, Altamore F, Jovanovic N, Windle E, Priebe S (2020) Indicators Associated With Job Morale Among Physicians and Dentists in Low-Income and Middle-Income Countries: A Systematic Review and Meta-analysis. JAMA Netw Open 3:e1913202–e1913202
20. Serghiou S, Goodman SN (2019) Random-Effects Meta-analysis: Summarizing Evidence With Caveats. JAMA 321:301–302
21. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J (2010) A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury: Clinical article. Journal of Neurosurgery JNS 112:1080–1094
22. Rockswold SB, Rockswold GL, Zaun DA, Liu J (2013) 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: Clinical article. Journal of Neurosurgery JNS 118:1317–1328
23. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE (1992) Results of a prospective randomized trial for treatment of

severely brain-injured patients with hyperbaric oxygen. J Neurosurg 76:929–934
24. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH (2001) Effects of hyperbaric oxygenation therapy on cerebral metabolism and intracranial pressure in severely brain injured patients. J Neurosurg 94:403–411
25. Harch PG, Fogarty PG, Staab PK, Van Meter K (2009) Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases J 2:6538
26. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, Aubrey C, Taylor D V, Staab PK, Van Meter KW (2011) A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder. J Neurotrauma 29:168–185
27. Harch PG, Andrews SR, Rowe CJ, Lischka JR, Townsend MH, Yu Q, Mercante DE (2020) Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. Med Gas Res 10:
28. Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S (2018) Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. BMJ Open 8:e023387